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Mast Cells in Experimental Skin Carcinogenesis*

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The changes in the epidermis induced by the application of 20-methylcholanthrene to the skin of mice have been investigated intensively in this hospital. These changes are accompanied by alterations in the dermis and the subcutaneous tissue, one of which is the appearance of numerous cells of various types including mast cells or tissue basophiles. The following account represents a systematic study of the mast cell reaction taking place in mouse skin undergoing the process of methylcholanthrene carcinogenesis.

PREVIOUS WORK

An increase in the number of mast cells has been observed in a great number of different pathological conditions (27), and a particularly massive increase was noted by the earliest workers on tar cancer. Borrel, Boez, and de Coulon (4) published a photomicrograph that gave a striking illustration of an intense mast cell reaction underneath a benign tar tumor in the skin of a mouse, as seen in a paraffin section stained with toluidine blue. They described these aggregations as "veritable naevi" and pointed out that cancer, which in Borrel's view is due to a virus, often arises from nevi of cellular elements belonging to the trophopigmentary system. The authors interpreted the mast cell reaction as "opening the door to all kinds of infections," and argued that the effect of tar on the skin is not directly carcinogenic but merely prepares the cells for the entrance of the cancer virus, a conception that is held in our time by Rous and his school.

A good illustration of a mast cell reaction was given also by Bierich, in a paper published at the same time (2). A number of other contemporary workers (11, 20, 28, 29) merely recorded an increased number of mast cells in the skin of mice after tar painting.

Borrell and his co-workers recorded in their paper the occasional occurrence of tumor-like masses in the tar-painted skin of mice. Such mastocytomas were noted also by Fabris (13) and by Schreuss (30) in tar-painted mice.

In this connection it is interesting to note the relatively frequent occurrence of spontaneous mastocytomas in the skin of dogs. Bloom (3) has described 5 such lesions in dogs aged from 5 to 15 years not suffering from skin cancer. This is of interest in connection with the fact that, of all the domestic animals of which a sufficiently large number of aged ones comes under the observation of veterinary pathologists, the skin is the site of carcinomas more frequently in dogs than in any other species (for statistical data see Cramer, 7).

After the early work had established an increase in the number of mast cells as a reaction of the mouse skin to tar, interest in the phenomenon waned, and in the more recent literature we have found only a paper by de Vinyals (10) that gives some further information on the subject. He describes differences in the morphological types of mast cells, to which he assigns a histioblastic origin, and interprets these differences as representing stages in the evolution of the mast cell.

There are probably several reasons to account for the loss of interest in the mast cell reaction. One is the lack of information concerning the function of these cells and the chemical nature of the substance responsible for their metachromatic staining. Recent work, to which reference will be made later in this paper, has partially removed this difficulty. Another reason is the fact, which will also be referred to again later, that mast cells are not easily recognized in routinely stained hematoxylin-eosin preparations, and that the extent and distribution of the reaction are subject to considerable variations.

* This investigation was aided by a grant from an anonymous donor.

MATERIAL AND METHODS

The treatment of the skin with methylcholanthrene was varied. As in our previous work on carcinogenesis, female mice of the Swiss strain obtained from Tumblebrook Farm were used. Methylcholanthrene in a 0.6 per cent solution in benzene (A. R. grade) was applied by a single stroke with a No. 4 brush to the skin of the back, over an area stretching from the nape of the neck to the middle of the back. To most of the animals examined only 5 applications had been given, at intervals of 3 weeks. This procedure results in the development of cancer in about 50 per cent of the animals within 9 months. The carcinogenic process thus induced differs in two main points from that following the technic usually employed hitherto: numerous applications, on alternate days. The total amount of methylcholanthrene applied is much smaller, so that the skin is not subjected to excessive doses acting continuously, and the average period of induction is even more prolonged. Cramer and Stowell (9) have shown that this results in a more gradual carcinogenesis, in which only one carcinoma, or at the most two, develops simultaneously in the painted area. In the rest of the treated skin extensive areas of epidermis frequently show little or only moderate hyperplastic changes, while in the immediate neighborhood of the carcinoma these changes may be very massive. It is thus possible to obtain in one axial section of the skin, which goes through the length of the treated skin area, a fully developed circumscribed carcinoma together with areas showing varying degrees of epithelial hyperplasia. Transverse sections give a different picture, showing the carcinoma in the center of the section. If sufficiently large the tumor occupies the whole central area of skin that has been exposed to the carcinogen, so that the carcinoma is frequently bordered by skin showing no or only slight degrees of hyperplastic changes. The importance for the study of the mast cell reaction of knowing the relation between the direction of a section and the direction of the brush stroke will be referred to again later.

The mast cell reaction was also studied in mice that, before the application of methylcholanthrene dissolved in benzene, had been subjected to a preliminary course of applications, on alternate days for 14 weeks, of methylcholanthrene dissolved in anhydrous lanolin. As recorded by us (31) prolonged treatment with an anhydrous lanolin solution of the carcinogen fails to induce epidermal hyperplasia, destruction of the sebaceous glands, or even epilation, and *ipso facto* skin cancer; at the end of such treatment the skin presents a normal macroscopic and histological appearance. We have since found that the skin of mice thus treated has become sensitized to the action of methylcholanthrene in benzene. In 2 experimental series, the results of which will be published in detail, 5 applications of methylcholanthrene in benzene at intervals of 3 weeks led to the development of hyperplastic changes and of skin cancer more rapidly and in a higher percentage of animals in such sensitized mice than in normal controls. In the present paper mice previously treated in this way will be referred to as "sensitized mice."

For a comparison with these 2 groups of experimental animals the mast cell reaction was studied also in mice in which carcinogenesis had been completed by application of the carcinogen on alternate days for 14 weeks. In all specimens in which a carcinoma had developed the animals were killed soon after the diagnosis had been made, so that late stages with extensive ulcerations were excluded. In addition to the skin of animals in which carcinogenesis had been completed, we have also examined normal skin and early stages of the epidermal hyperplastic response that developed 3 or 4 weeks after single or repeated applications of the carcinogen dissolved in benzene. Altogether the skins of more than 150 mice were examined microscopically for the data on mast cells.

The skin exposed to the action of methylcholanthrene and the adjacent normal skin was removed in one piece, stretched on a piece of mica, and fixed for 12 to 24 hours in 10 per cent formalin. Microscopic examination was carried out:

1. On frozen sections (a) unstained in ultraviolet light, and (b) stained with aqueous toluidine blue for mast cells.

2. In paraffin sections after the formol-fixed skin had been treated with a 2.5 per cent solution of potassium bichromate for 2 days. As a rule both transverse and axial sections of the skin were prepared. In order to obtain microscopic preparations representing approximately the same areas of skin for these two technics, the following procedure was followed. The formol-fixed skin was about 2.25 cm. broad and 3.5 cm. long, tapering towards the posterior end. From either the anterior or the posterior part two narrow transverse strips were cut in such a way as to include part of a carcinoma when present. One strip was used for frozen sections, which were examined unstained in ultraviolet light and, stained with toluidine blue, in ordinary light. The remaining larger portion of the skin was halved by cutting it axially along the mid-line. The cut edge of each half would usually pass through any carcinoma present in the skin. One of these strips was again used for frozen sections in the same way as one of the transverse sections. The second transverse and the second

axial sections were placed in 2.5 per cent potassium bichromate for 2 days, dehydrated, embedded in paraffin, and cut. Alternate paraffin sections were stained either with hematoxylin-eosin or with toluidine blue. This technic provided long strips of skin going through the whole length and the whole width of a skin area exposed to the carcinogen, and, as already mentioned, made it possible to get a fairly comprehensive view of the changes taking place there.

While it is known that watery fixing fluids are not suitable for the study of mast cells in most species of animals, including man, because the metachromatically stained granular material in the cells is incompletely precipitated by the watery fixative, it has also been recognized that watery fixatives give good results in the mouse and the rat, presumably because the metachromatically stained material in these two species is chromatically after both the watery and the alcoholic fixatives. In some mast cells the material is water-soluble, and in these the granules are not stained metachromatically after fixation in the watery formol solution but do retain their metachromatic staining when fixed in the alcoholic formol solution. Thus from each individual specimen of skin a number of different preparations were made, never less than 2, but sometimes 4 or even more. They differed in the areas of skin examined, the method of fixation, or the technic of microscopic examination. Our observations and conclusions are thus based on the examination of many hundreds of preparations.

Normal Skin

Mast cells are present in the normal dermis of the mouse, dispersed irregularly in the tissue, most of them lying in the deeper part of the dermis below the level of the sebaceous glands while only a few small ones are seen near the epidermis. In view of this irregular distribution it is more instructive to compare their numbers in small areas of the dermis, where they are frequent, than to count them in large areas. In strips 0.2 mm. broad, which cover the greater part of the dermis in histological sections, their maximal number in areas 0.5 mm. long varied in different animals from 10 to 20 in transverse sections and from 6 to 10 in axial sections.

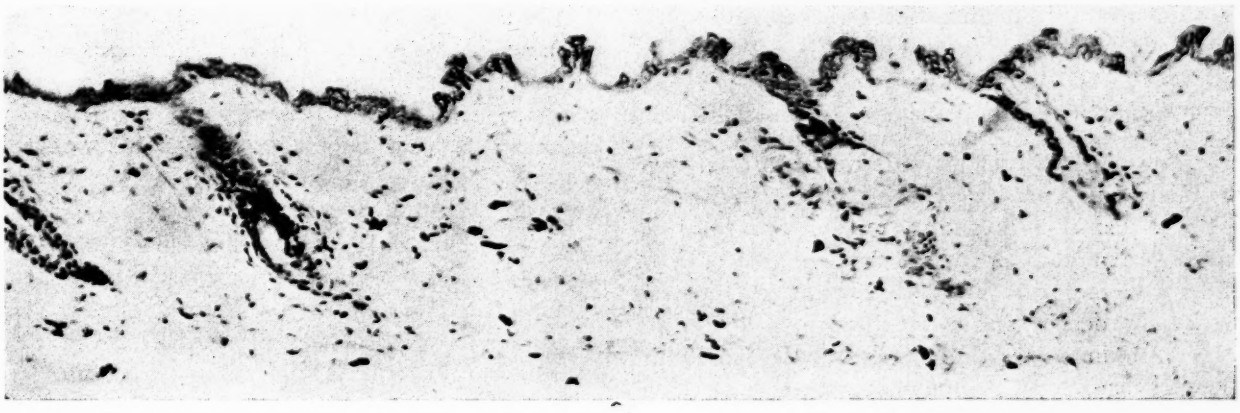

Fig. 1.—Axial section of dorsal skin of a normal mouse. Fixation—10 per cent aqueous formalin, mordanted 2 days in 2.5 per cent potassium bichromate. Stained with aqueous solution of toluidine blue for mast cells, which appear as isolated black spots in the photograph. Mag. × 165.

less soluble. Since we wished to compare, in the same individual skin sample, the appearance of frozen sections in ultraviolet light, particularly with reference to substances soluble in alcohol, with the changes visible in paraffin sections, we were restricted in these observations to the use of such a watery fixative as formol. Comparative observations were made, therefore, on tissues fixed in a solution of 10 parts of formol and 90 parts of absolute alcohol. For this purpose the methylcholanthrene-treated skin was removed in one piece and then halved by an axial section going along the mid-line. One half was fixed in the watery formol solution, and the other in the alcoholic formol. The results will be described in detail later in the paper; here it is sufficient to state that the two methods of fixation disclosed differences in the chemical nature of the metachromatically staining substance deposited in the granules of different mast cells. In the mouse this substance is water-insoluble in most mast cells, so that the granules are stained meta-

The sizes and shapes of the mast cells differ somewhat even in one small area of dermis, as illustrated in Fig. 1. Some are stretched out to a narrow band from 8 μ to 15 μ long, and from 1 μ to 3 μ broad; others are oval with diameters such as 8×6 μ, or 12×3 μ. The cells are uniformly packed with fine, discrete, metachromatically stained granules in preparations stained faintly with toluidine blue. Sections to be used for photomicrography were intentionally

overstained with toluidine blue in order to bring out the epithelial structures of the skin; as a result, the contents of the mast cells, when these are fully loaded with their specific granules, appear as a solid mass in the photomicrographs.

The data given above refer to paraffin sections. In frozen sections the number of mast cells is greater, owing to the greater thickness of the sections. The dimensions of individual cells are also larger: from 10 μ to 15 μ in length for the small cells, from 20 to 30 μ for the large ones, with corresponding increases in width from 3 μ to 20 μ. The granules are more widely separated from each other than in the paraffin sections. This difference in dimensions is due to the shrinkage that the cells undergo in passing through alcohol and xylol for paraffin embedding. In the normal skin the mast cells are almost always well filled with granules. Scattering of granules by the cells to the surrounding tissue is an infrequent phenomenon.

Skin with Carcinogenesis Completed

Passing now from the normal skin to the final stage of the carcinogenic series, namely a methylcholanthrene-treated skin presenting one or two fully developed carcinomas together with varying degrees of epidermal hyperplasia and accompanied by a broadening of the dermis and wide dilation of the blood vessels, striking changes are found in the mast cells. These changes affect their number, their distribution, and their morphological and histochemical properties.

Their number is always increased, but the degree of this increase varies greatly in different animals. Their distribution, their size, their shape, and their staining reaction in one individual specimen of skin exposed to the carcinogen are not homogenous (Fig. 2). As a rule, there are very few mast cells in the carcinoma itself and those present are found lying mostly in the peripheral parts of the tumor, which represent its most newly formed portion, and appear to undergo a process of disintegration. Sometimes they are completely absent, but if the stroma is very abundant these cells may be slightly more numerous. The neoplastic area of the skin differs in this respect from the hyperplastic nonneoplastic epidermis, where the mast cells are seen in large numbers in the connective tissue, running up towards the epidermis between the massive epithelial pegs and down toward the subepithelial connective tissue (Figs. 3 and 4). The mast cells may be scattered irregularly through the dermis, or packed together in small aggregates (Fig. 5). Very occasionally these aggregates may be so large as to form a definite nodule visible to the naked eye. These are the so-called mastocytomas, of which we have observed two. Since very frequently the carcinoma has developed within an area of hyperplastic epidermis, such areas may abut against the carcinoma. Under these conditions the dense aggregation of mast cells in these hyperplastic areas contrasts strongly with their rarity in the contiguous carcinoma (Fig. 2).

When a small early carcinoma that has not invaded the width of the dermis is present, numerous mast cells may be seen at the base of the tumor; the carcinoma then presents a picture of being surrounded by a semicircle of mast cells while harboring only a few or none in its stroma. On the whole it can be said that the increase in the number of mast cells runs parallel to the degree of the noncancerous epithelial hyperplasia present in a given specimen of skin. In previous papers we have given illustrations of a carcinoma developing in a skin that elsewhere shows only slight degrees of hyperplastic changes. In such a skin the mast cell reaction is, as a rule, least pronounced. A weak mast cell reaction was found also in the few carcinomas that appeared after a very short period of induction. Since a carcinoma can develop rapidly in the absence of a massive mast cell reaction, this reaction cannot well be interpreted as favoring or accelerating the process of carcinogenesis.

There is thus a great diversity in the mast cell reaction, as there is a great diversity in the carcinogenic response in the skin of different animals. This necessitates a more detailed account of the morphological and histochemical appearances of the mast cells. Since most of our observations had been carried out with the watery fixative, for reasons given earlier in this paper, these will be described first.

Morphological changes.—As stated earlier in this paper combinations of fully developed carcinomas with varying degrees of hyperplastic changes in the epidermis are seen in axial sections that go through the whole skin area exposed to the carcinogen, while in transverse sections they may be absent. Accordingly the mast cell reaction may be very strong in an axial section, but weak in a transverse section of skin from the same animal; for in the transverse section the carcinoma occupies the whole skin area exposed to the carcinogen, and abuts against skin showing only slight degrees of epidermal hyperplasia or even none at all. There are also great differences now in the sizes and shapes of the mast cells, and in the extent to which they are loaded with granules. Many are as fully loaded as those of the normal skin, but there also are small ones that are only partially loaded with granules, and some that are almost empty. Reference will be made presently to the fact that after fixation in a watery formol solution the granules may also differ in their staining reaction with toluidine blue, while

FIG. 2.—Methylcholanthrene-treated mouse skin showing a portion of a carcinoma at left and a massively hyperplastic epidermis at right. Preparation as that of Fig. 1. Stained with toluidine blue and eosin. Note dense accumulation of mast cells (black spots in photograph) beneath hyperplastic areas and relative absence of such cells in carcinoma. Mag. × 70.

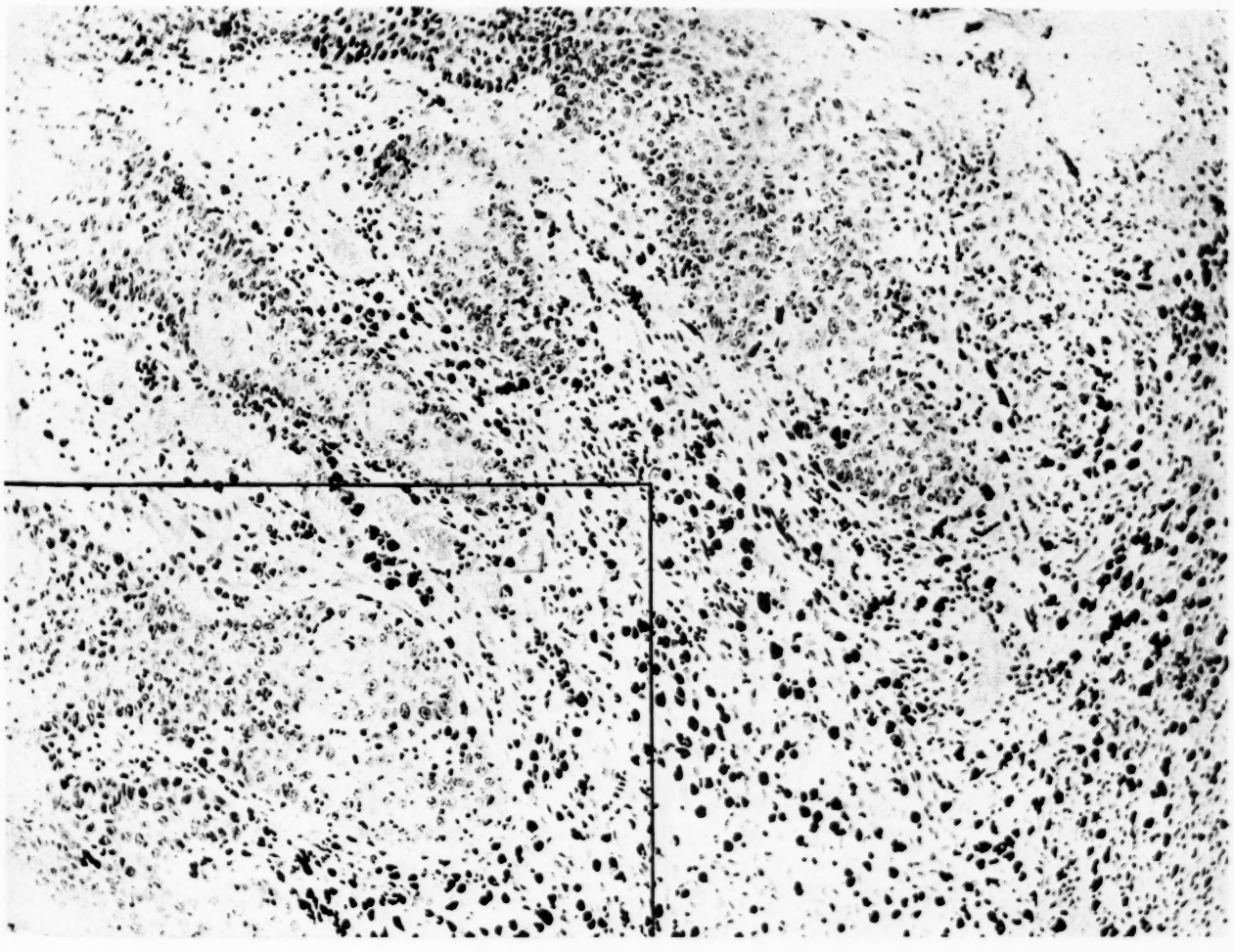

FIG. 3.—Early mast cell response beneath massively hyperplastic epidermis. This scattered distribution occurred after 4 applications of methylcholanthrene at 2 week intervals. Section prepared as for Fig. 1. Mag. × 140.

after fixation in an alcoholic formol solution this difference is not present. The gradual filling up of the cells with their specific granules suggests the various stages of a secretory process. This point will be discussed again later, when the mast cell reaction is discussed in detail with reference to its bearing on the origin of these cells. The scattering of granules, which is most clearly seen in paraffin sections in the neighborhood of the large cells, is probably an artefact, since in frozen sections that have been mounted carefully such scattering is an infrequent phenomenon.

Histochemical changes.—The histochemical changes manifest themselves in two ways. The mast cells of normal skin do not fluoresce in ultraviolet light, but when a strong mast cell reaction has developed underneath an area of massive epithelial hyperplasia in response to the treatment with methylcholanthrene, certain groups of mast cells show a strong golden-brown fluorescence that contrasts strikingly with the blue fluorescence of the hyperplastic epidermis. Not all the mast cells, however, exhibit this fluorescence; those in the deeper parts of the dermis that are more remote from the hyperplastic epidermis do not. It is restricted mainly to the cells lying between the massive epithelial pegs of hyperplastic epidermis. This golden-brown fluorescence is impressive as an indication of the presence in relatively large amounts of a new substance localized in the immediate neighborhood of the hyperplastic epithelium and restricted to that area.

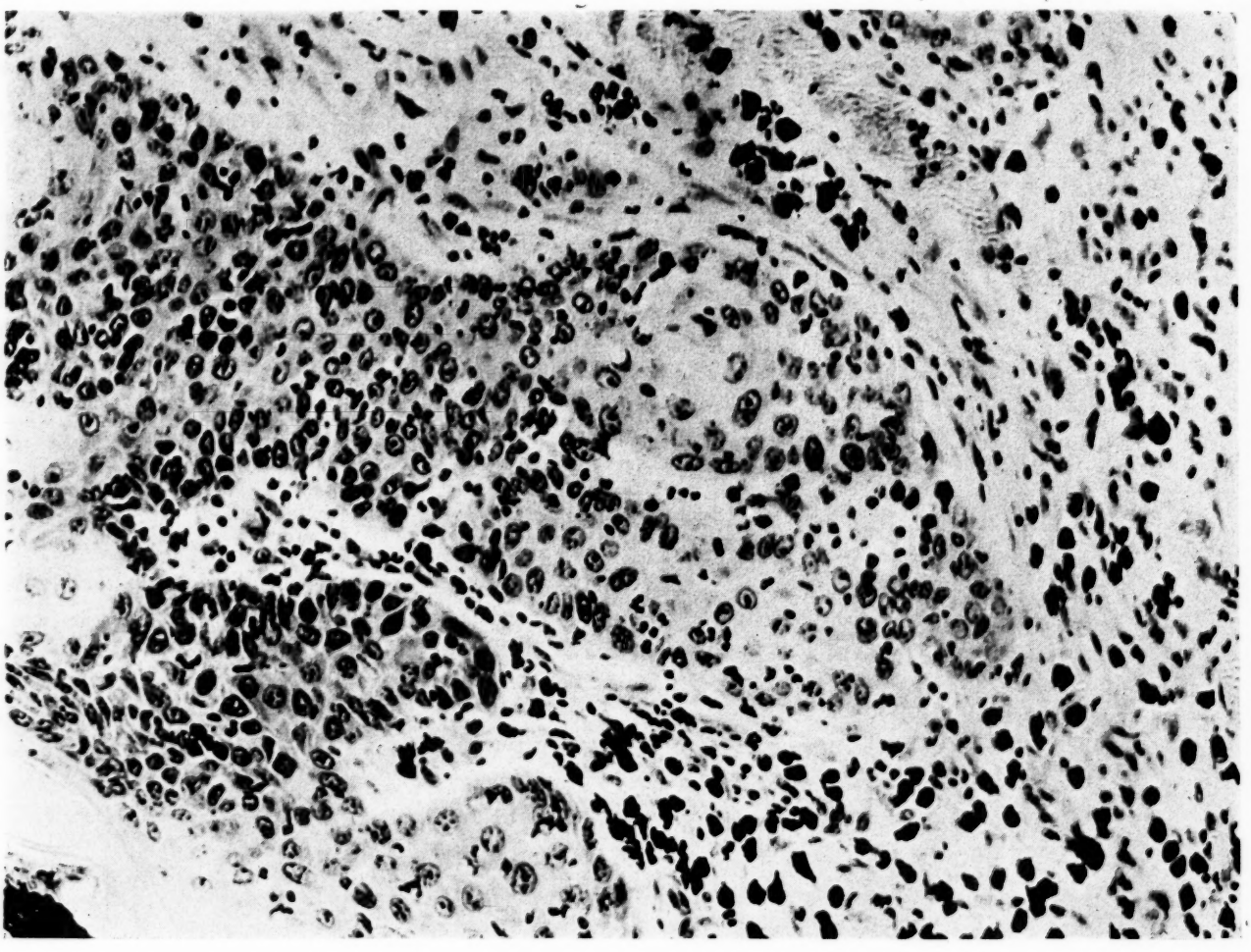

FIG. 4.—The outlined portion of Fig. 3 at higher magnification. Mast cells, appearing as irregular solid black spots, tend to be accumulated near pegs of hyperplastic epithelium. Mag. × 285.

The second type of histochemical change refers to differences in the metachromatic staining of the granules that have been mentioned in the preceding paragraph. Cells are present having the same small size and shape as the typical mast cells and similarly filled with fine granules, but these granules do not stain metachromatically with toluidine blue (Figs. 5 and 6). These cells with granules that take the blue color of the stain will be described as "ametachromatic" mast cells. The possibility has been discussed earlier in this paper that this phenomenon may indicate the

existence of two types of the metachromatically staining substance deposited in the granules of the mast cells; one soluble, the other insoluble, in water.

In addition to these ametachromatic mast cells there are cells of the same size and shape as typical metachromatic mast cells in which, however, the granules between the massive epithelial pegs, where they are arranged in a fairly definite pattern. The cells poor in granules lie nearest the epidermis. A little deeper the cells are partially filled, and still deeper, completely filled with granules that stain blue. Further down the cells are filled with granules that stain

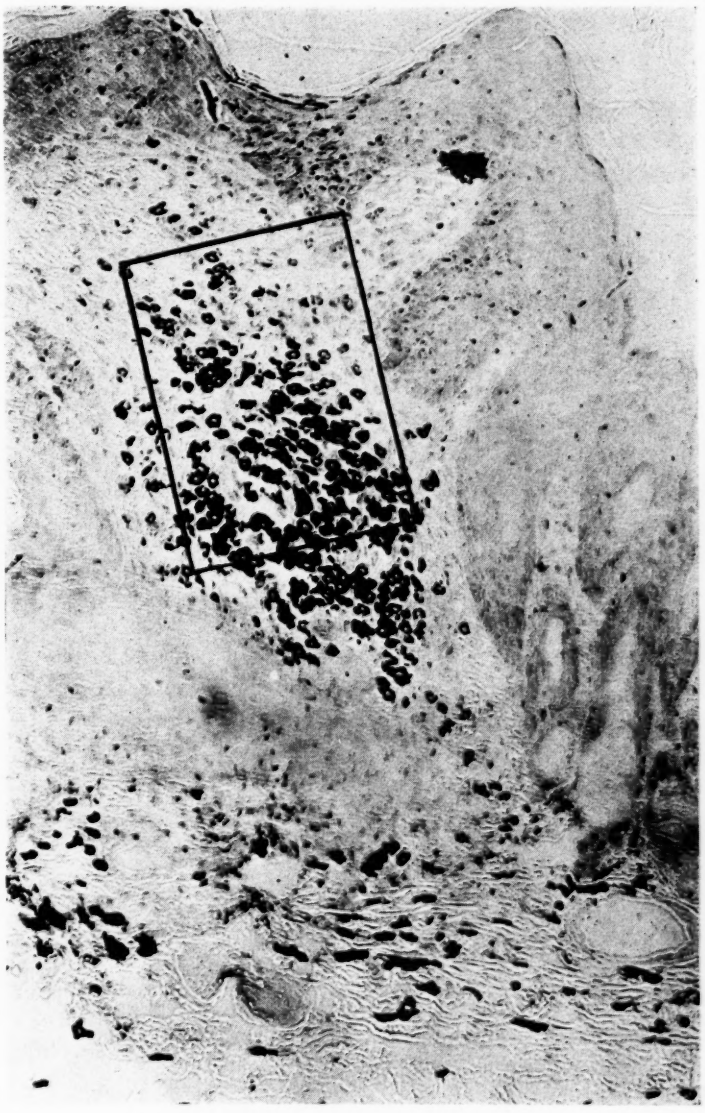

FIG. 5.—Dense cluster of mast cells in connective tissue projection between pegs of massively hyperplastic epidermis. From a methylcholanthrene-treated animal bearing a carcinoma in another area of its skin. Nodule composed entirely of ametachromatic cells and of cells with only a few granules, *i.e.*, agranular cells. The large cells deep in the dermis stained metachromatically. Same technic as Fig. 1. Mag. × 170.

are greatly diminished in number and stain either blue or only faintly metachromatically (Fig. 6). Cells of this type will be described as "agranular" mast cells.

These two types of atypical cells, the ametachromatic and the agranular, are intermixed and occasionally lie close together with typical mast cells. They are most frequently seen in the more superficial parts of the hyperplastic skin, especially in the connective tissue metachromatically and surround, but do not obscure, the nucleus. In the deeper parts of the dermis the mast cells are so completely loaded with granules that their nuclei are not visible. In the deepest part of the dermis the largest and most fully loaded cells are encountered.

These morphological appearances can be interpreted *a priori* in two ways. The beginning of the reaction

may be conceived as represented by the small agranular cells near the periphery. As they move down to the deeper layers these cells form granules, which gradually become loaded with the metachromatic substance. The cells increase in size as the load of metachromatic material increases, thus forming the large intensely stained mast cells in the deeper layers of the dermis. Or one may assume that the fully loaded mast cells represent the beginning of the reaction. They increase in number in the deeper layers of the epidermis, as the result of a process that is as yet obscure. They move upwards in the connective tissue towards the surface of the dermis and in doing so lose their granules, diminish in size, and eventually become small agranular mast cells. These two interpretations have an opposite significance.

FIG. 6.—Higher magnification of area outlined in Fig. 5. A progressive increase in number of granules and intensity of granule staining may be observed beginning from the upper right corner, near epithelium, and proceeding downward toward dermis. Cells such as those indicated by arrows are referred to as "agranular" mast cells. With the exception of one central cell, indicated at M, all cells in this field stained ametachromatically. Preparation as Fig. 1. Mag. × 680.

According to the conception first mentioned the mast cells form their metachromatically staining material within the dermis. This material, as will be explained later, belongs to a group of chemically closely related substances distinguished by the property of being stained metachromatically by certain basic dyes. It has been called for brevity the "chromotrope substance." The mast cells continue to form this material, with a resultant increase in their size and in their load of chromotrope substance. The second conception compels us to assume that mast cells, fully differentiated, deeply loaded with chromotrope substance, and abnormally large, have been carried to the dermis, presumably by the blood, and have emigrated from the blood vessels. As will be pointed out later, there is no convincing evidence for such an origin from the blood. On the other hand, recent studies on the chemistry of the chromotrope substance in the mast cells have identified it as a polysulphuric acid ester of a high molecular polysaccharide, closely related chemically to similar sulphuric acid esters present in connective tissue. On chemical grounds, therefore, the first mentioned conception of a tissue origin of the mast cells presents no difficulties. This subject will be discussed again later.

Whatever the correct explanation of the origin of the mast cells in our material may be, there appears to be an interesting correlation between these changes and the presence or absence of a golden-brown fluorescence in ultraviolet light, in the sense that the fluorescence is exhibited mainly by the more atypical cells nearest the surface. This point is being further investigated. Here attention is drawn to the existence of these variations and deviations from the mast cells of the normal skin as an indication of a great increase in the functional activity of these cells in methylcholanthrene-treated skin exhibiting a massive mast cell reaction.

Intermediate Stages

The intermediate stages of the mast cell reaction were studied by examining the skin of mice exposed to one or to several applications of the carcinogen. The animals were killed at varying intervals after the last application, when epidermal hyperplasia had appeared but before this change had culminated in the development of a carcinoma. Sections of the skin made along the whole breadth or length of the painted skin area showed, as has been illustrated in previous papers, circumscribed areas of epidermis with varying degrees of hyperplasia. These hyperplastic areas were either single, and thus surrounded by skin showing little or no epidermal changes, or they were multiple and separated from each other by stretches of almost normal skin. In these intermediate stages there was also a correlation between the site and the degree of epithelial hyperplasia and the site and degree of the mast cell reaction. In individual samples of skin the mast cell reaction was more intense where the epithelial hyperplasia was most pronounced, while it was less pronounced or weak where the hyperplastic change was weak. The mast cell reaction sets in, therefore, before the malignant change has taken place, and not as a result of this change. This accounts for the fact that when the process of carcinogenesis has been completed the mast cell reaction is not limited to the immediate neighborhood of a carcinoma but is present also in those parts of the skin remote from the carcinoma, in which pronounced hyperplastic changes are present. With the technic employed by us, in which an extensive area of the skin is exposed to the carcinogen, such hyperplastic changes are frequently extensive and the carcinoma develops in a sharply circumscribed area of this extensively hyperplastic epidermis. But occasionally the preliminary hyperplasia is restricted to a small area, indicating a certain degree of resistance on the part of the skin to the carcinogen. When a carcinoma develops under such conditions it is surrounded by skin showing only slight degrees of hyperplastic changes and with it a weak mast cell reaction.

Mast Cell Reaction in Resistant Mice

With our technic of applying minimal effective doses of the carcinogen by limiting the number of applications, cancer is induced in about 50 per cent of the animals within a period of 9 months. The animals that were negative at the end of the experiment were, therefore, more resistant, and showed either no macroscopic changes in the skin or a slight roughening with slight epilation and, at most, a small delicate papilloma, which had shown no evidence of increasing in size during the last few months. When such resistant mice are killed for microscopic examination the skin may show either very slight and insignificant changes or, in animals with the slight macroscopic lesions, a mild or moderate degree of hyperplasia, which however, is not sufficiently advanced to be called precancerous. But in this latter group, staining with toluidine blue discloses a massive mast cell reaction. Figs. 7, 8, and 9 illustrate the extent of this reaction in 2 resistant mice killed $11\frac{1}{2}$ months after the first application of methylcholanthrene. These findings in resistant mice, together with the absence of a massive mast cell reaction in susceptible mice, *i. e.*, animals in which a carcinoma appears after a very short period of induction, are significant. They indicate that the mast cell reaction is associated with

a defensive mechanism against the development of skin cancer.

FIG. 7.—Mast cell response in skin of mouse "resistant" to carcinogenesis by methylcholanthrene. Treatment of section as Fig. 1. Mag. × 60.

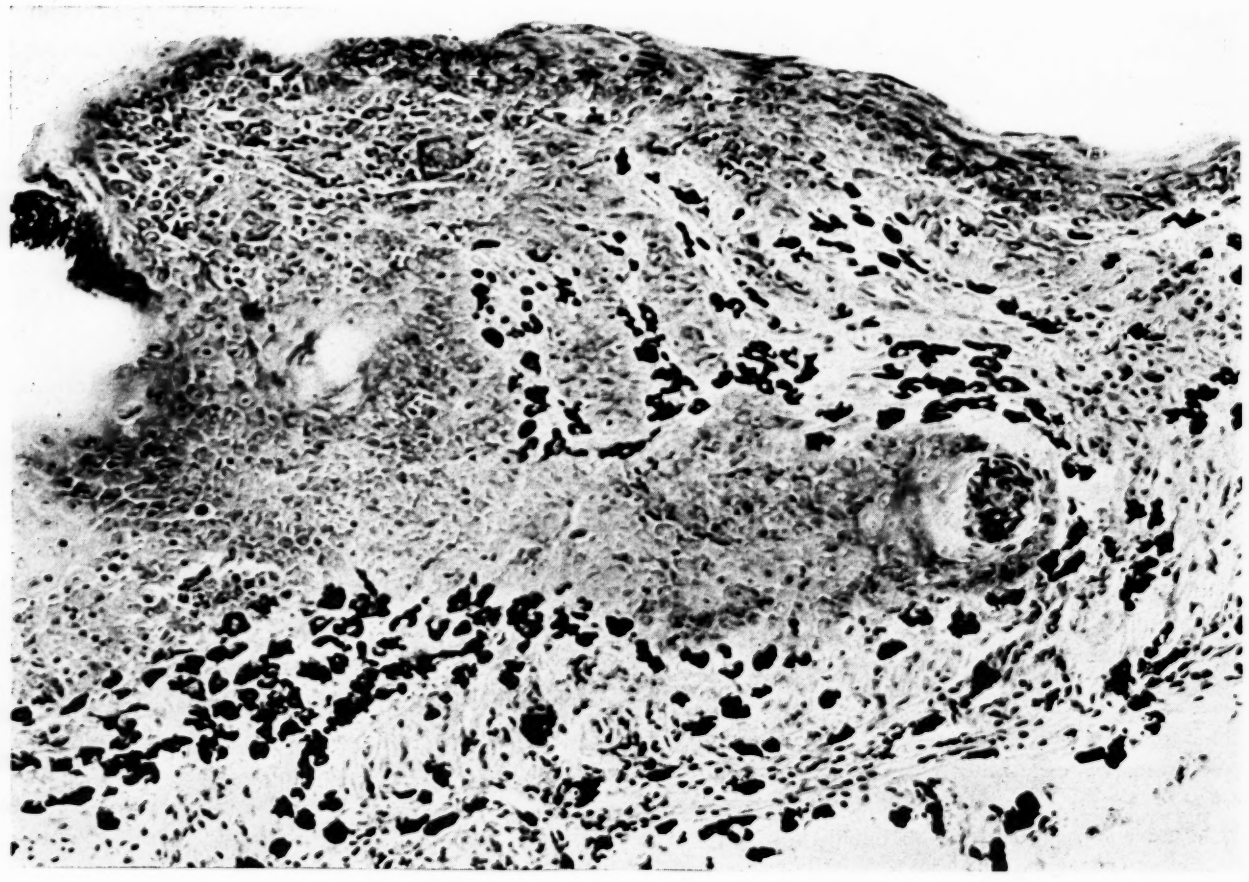

FIG. 8.—High power photograph of right end of area figured in 7. Note intimate association of mast cell accumulations to pegs of hyperplastic epithelium. Mag. × 220.

ON THE ORIGIN OF MAST CELLS

Two significant findings of a negative nature may be added that have a bearing on the question of the origin of mast cells in this reaction. No mitotic figures have been observed in the mast cells, so that the increase in their number cannot be attributed to proliferation of the relatively few generally seen in the skin. No evidence was obtained that could be interpreted as indicating that the mast cells had emigrated from the blood vessels, nor did their distribution in the subcutaneous tissue suggest the likelihood of a hematogenous origin. Furthermore, mast cells were generally not more numerous in the immediate neighborhood of the dilated blood vessels than in the more

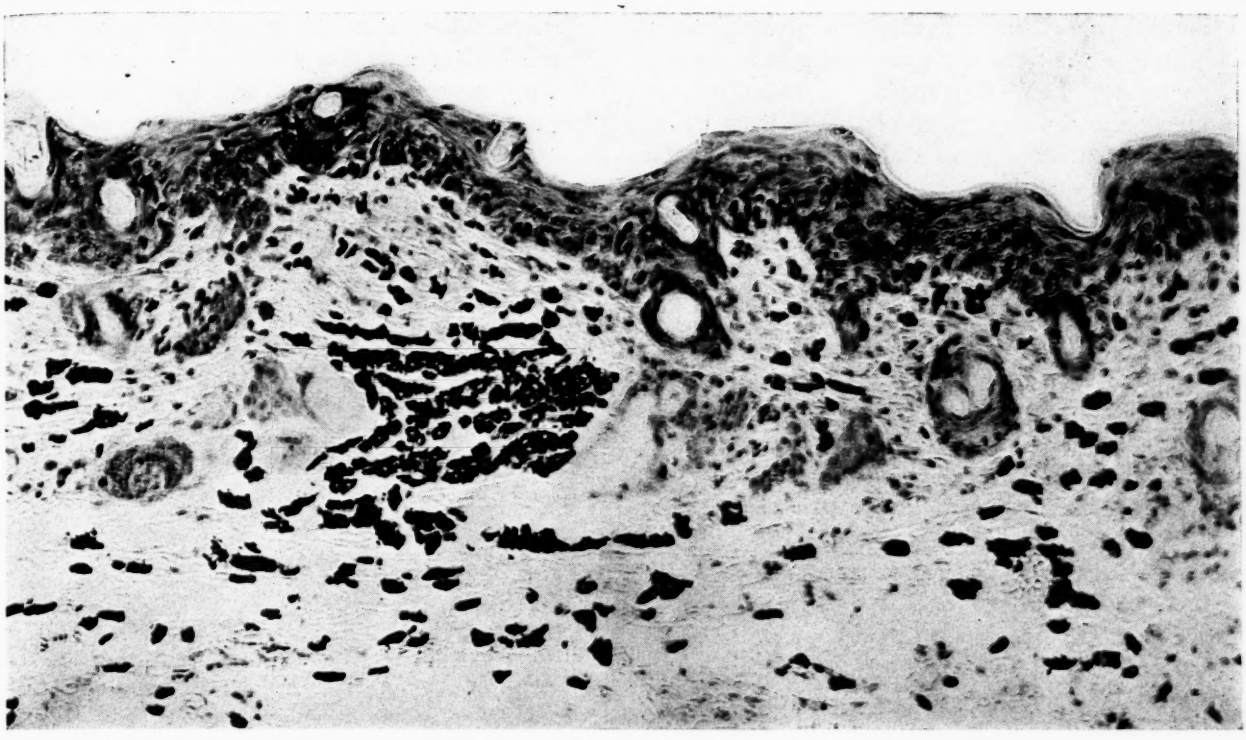

FIG. 9.—Methylcholanthrene-resistant mouse skin showing local nodular mast cell response. Such a nodule may be regarded as a small mastocytoma. Preparation as Fig. 1. Mag. × 600.

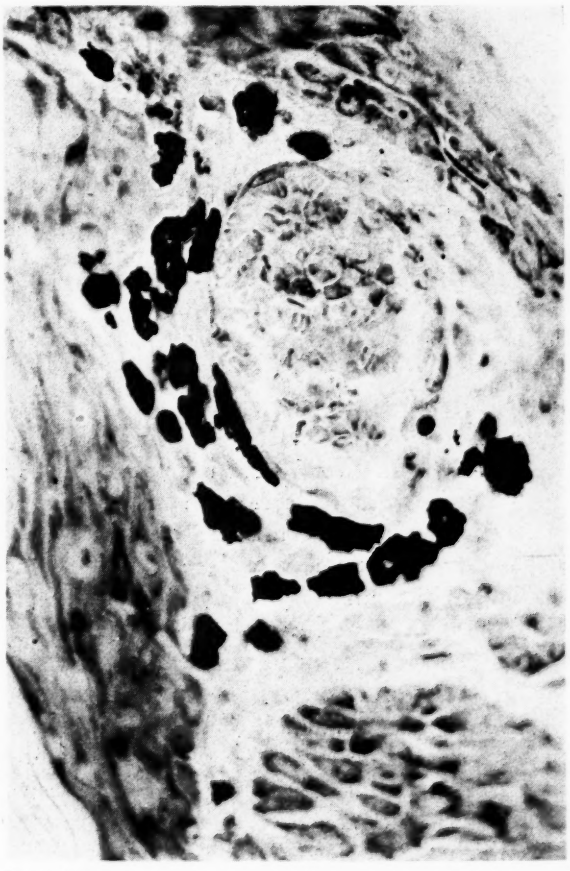

FIG. 10.—Large tissue mast cells surrounding dilated venule in hyperplastic skin bordering on methylcholanthrene-induced carcinoma. Preparation as Fig. 1. Mag. × 511.

remote parts; on the contrary, where these cells were aggregated, as they sometimes are, it was at a distance from the blood vessels. Occasionally large, fully loaded mast cells were seen encasing a small blood vessel, as shown in Fig. 10, but such findings were infrequent. This contrasts with the distribution in the normal skin of man and in such pathological conditions as urticaria pigmentosa, where the blood vessels are stated to be often surrounded by a mantle of mast cells (16, 23). In methylcholanthrene-treated skin where mantles of mast cells were encountered around the dilated venules there were no cells intermediate in type between these large cells and the very much smaller basophiles of the blood. Our observations, then, agree with the conception of a histogenous origin of the tissue mast cells, in the sense that an increase in the tissue mast cells results from a process taking place locally within the tissue.

The Appearance of Mast Cells after Alcoholic Fixation

The results described so far refer to material fixed in a 10 per cent aqueous solution of formol and subsequently treated with an aqueous potassium bichromate solution. After fixation in a 90 per cent alcoholic solution of formol, followed by transfer to absolute alcohol, the mast cells show in most respects the same morphological appearances. They are present in about the same number; they show the same patchy

distribution, closely related to the degree of hyperplasia; they exhibit the same differences in shape and size; and they show the scattering of metachromatic granules even more than material fixed in a watery formol solution. The main difference relates to one point; namely, that nearly all the mast cells seen after alcoholic fixation are filled with granules that stain metachromatically, though there may be slight differences in the degree of the metachromasia and occasionally ametachromatic cells are observed. It will be recalled that the ametachromatic mast cells described in aqueous-formol fixed skin are localized in the most superficial parts of the dermis, where the typical metachromatic mast cells are infrequent. In material fixed in the alcoholic formol solution aggregates of numerous mast cells are seen also in those superficial parts of the dermis, but they are filled with granules that stain metachromatically.

It may be said, therefore, that the ametachromatic type of mast cell seen after a watery fixative is an artefact. Nevertheless the production of this artefact by a watery fixative is of significance, for it shows that in the mouse the metachromatically staining material in the mast cells—the chromotrope substance—is not homogenous. Some of it is water-soluble, like the chromotrope substance of the mast cells in most other species, while another part is water-insoluble. The difference between the mast cells in the superficial parts of the dermis underlying an area of pronounced epidermal hyperplasia and those in the deeper parts of such a dermis, which after a watery fixative manifested itself in the absence or presence of metachromatic staining of the granules, finds thus an explanation in the solubility in water of the chromotrope substance present in those two types of mast cells. In the metachromatic type the chromotrope substance is insoluble in water; in the ametachromatic type it is soluble. In the mouse, therefore, the study of the mast cells in skin fixed by a watery fixative has the advantage of revealing differences in the functional activity of these cells that are not disclosed so clearly by an alcoholic fixative.

Mast Cells in Routine Hematoxylin-Eosin Preparations

Mast cells are not easily recognized in routine hematoxylin and eosin-stained preparations unless they are abnormally large or are aggregated in considerable numbers. Fig. 11 illustrates the appearance of such an aggregation of small mast cells in a methylcholanthrene-treated skin fixed in Bouin and stained with hematoxylin and eosin. But the routinely stained skin always fails to give a correct impression of the extent of the mast cell reaction, even when this is massive. As stated earlier this has probably been responsible for the lack of attention given to this phenomenon, for an increase in the mast cells had been already observed by some of the early workers on tar cancer. It had also been noted by one of us (W. C.) in routinely stained hematoxylin-eosin preparations of tar-painted mouse skin.

Mast Cells in Hyperplastic Conditions of the Human Skin

In human skin cancer an increase in the mast cells has been occasionally observed, but seems to have received little systematic attention. At any rate we have found no reference to this reaction in a number of pathology and dermatology textbooks. An essential similarity between the mast cell reaction in the skin of man and that of the mouse was found on examining a few specimens of human skin showing a precancerous epidermal hyperplasia occurring in such conditions as senile hyperkeratosis and Bowen's disease. Fig. 12 is submitted as illustrating this similarity. It is of a relatively extensive hyperkeratotic lesion removed from the face of a man aged 70 with numerous senile hyperkeratoses. The epidermis showed a massive precancerous hyperplasia. In man the mast cells are more delicate, more slender, and more finely granular than in the mouse, and the chromotrope substance is more soluble in water, so that an alcoholic formol solution is preferable as a fixative. But in this and in the other precancerous epithelial hyperplasias examined the mast cells were numerous, resembling in this respect the corresponding conditions studied in the mouse skin.

DISCUSSION

In this paper we have limited ourselves to a description of the changes in the mast cells found in skin where, as a result of exposure to a potent carcinogen various degrees of epithelial hyperplasia had developed. This mast cell reaction must not, however, be interpreted as a specific reaction to a carcinogen. A massive increase in the mast cells of the skin has been observed in a number of other conditions also. According to Staemmler (31) the number of mast cells in the cutis increases with the amount of fine collagenous fibers present in the connective tissue; they are absent or rare in acute inflammatory conditions, in young granulation tissue, and in coarsely fibered sclerotic connective tissue. He attributes to the mast cells the function of supplying the cement substance (*Kitt-Substanz*) of the ground material, within which the collagen fibers develop. This view has received confirmation in the recent work of Sylven, to be discussed presently.

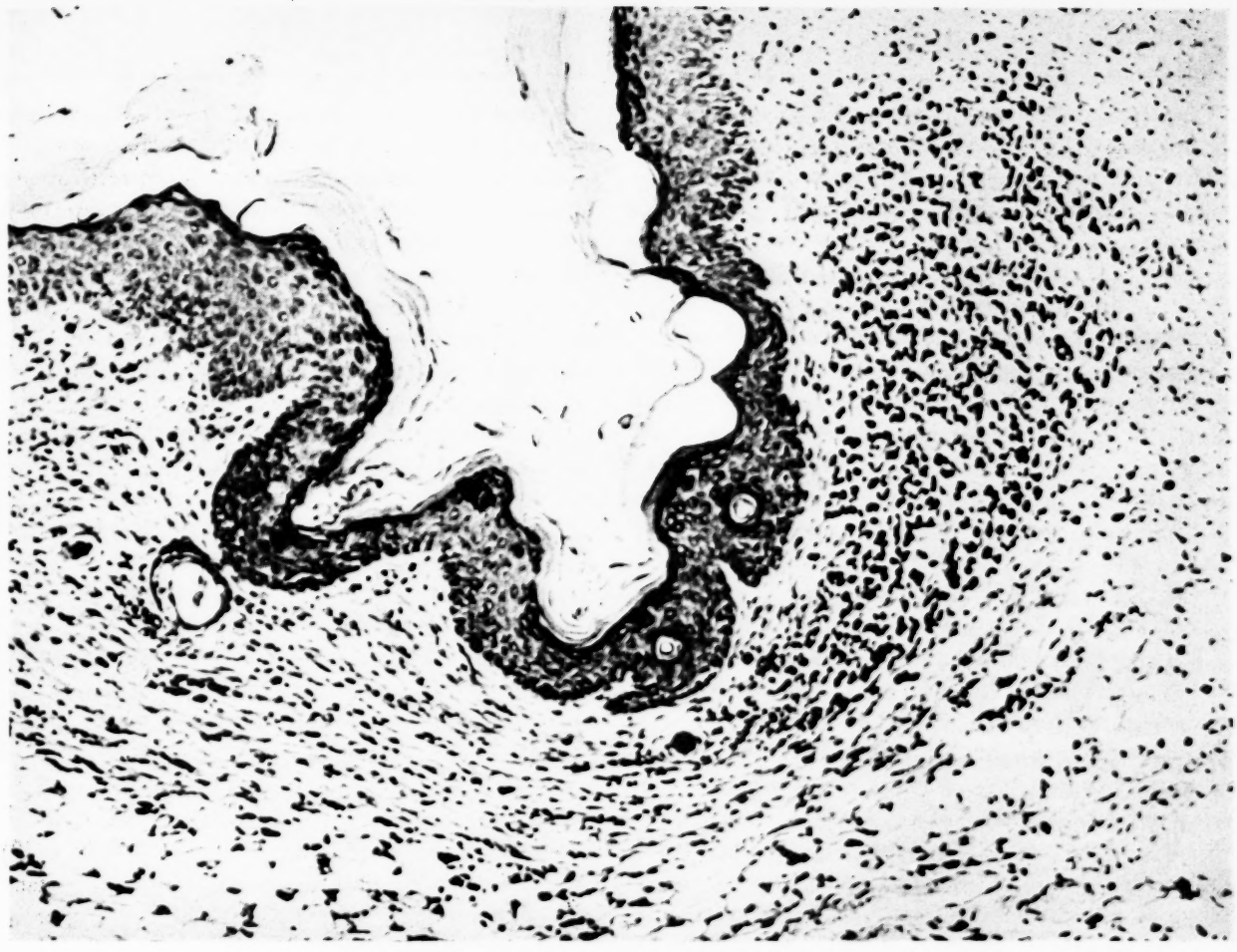

FIG. 11.—Intense mast cell response occasionally seen in routine hematoxylin and eosin preparations of methylcholanthrene-treated mouse skin. Bouin fixation and hematoxylin and eosin staining. Mag. × 165.

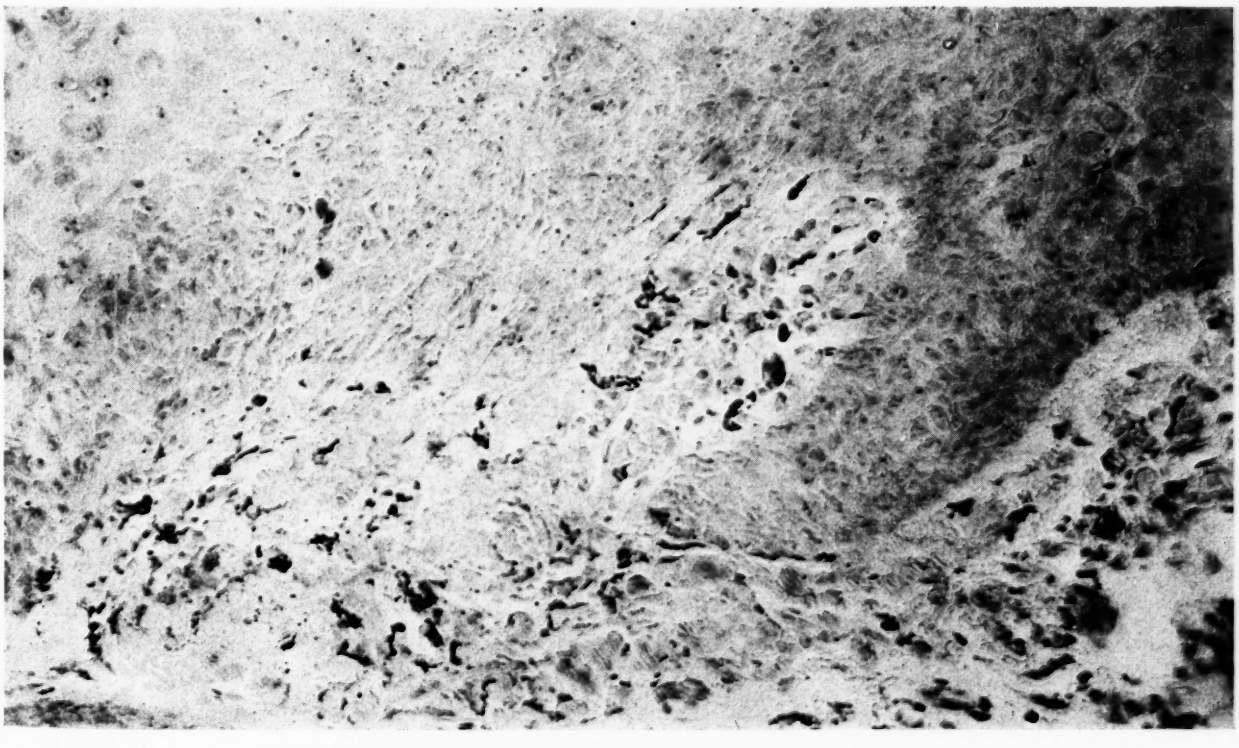

FIG. 12.—Mast cell accumulation immediately adjacent to hyperplastic epidermis of senile keratosis from a man of 70 years. Mast cells smaller and much more delicate than those of mouse. Photomicrograph taken with filter that renders metachromatic material dark. Formol-bichromate fixation. Toluidine blue staining. Mag. × 300.

Of other pathological conditions there appears to be only one in which an increase as massive as that observed in our material has been found. This is a rare skin disease, urticaria pigmentosa. To judge from an illustration in McCarthy's *Histopathology of Skin Diseases* (23) the increase may be as great as the reaction found in our material, although urticaria pigmentosa has no obvious relationship to skin cancer.

Further investigations are required to determine whether types of epidermal hyperplasia that do not proceed to the development of cancer—in other words nonprecancerous epidermal hyperplasias—are accompanied by an increase in the number of mast cells comparable in intensity to the reaction found in the precancerous types. Michels (27), in his comprehensive review of the literature on mast cells published in 1938, states: "The causative factor for the numerical increase of tissue mast cells is unknown." At that time the same statement might also have been made concerning the function of the mast cells, but since then a number of important observations on the chemical nature of their metachromatic granules have been published that have a bearing on this problem.

Lison (21, 22), in a series of papers published from 1932 to 1935, showed that the metachromatic color change of toluidine blue is induced specifically by a group of substances closely related chemically in so far as they are all polyesters of an organic radical, consisting of a high molecular polysaccharide, with several molecules of sulphuric acid. The term "chromotrope substance" is used to designate this group. Subsequently Jorpes (17) identified heparin as belonging to this group of sulphuric acid esters, and together with Holmgren and Wilander (15, 18) brought evidence to show that the granules of mast cells owe their metachromatic staining to the presence of such organic sulphuric acid esters, which have a heparin-like action. These results lend support to the concept formulated by earlier workers that mast cells have the property of forming a specific secretion. According to Holmgren (16) free chromotrope substances are present in embryonic connective tissue, but not in fully developed connective tissue. But it appears in each adult tissue when growth processes are induced in them, as in the regeneration of the epidermis in wound-healing. In that condition Sylven (33) found that chromotrope substances appeared within 24 hours between the squamous cells of the epithelium and even within their cytoplasm. At the same time the mast cells lost their granules and an increased number of such mast cells poor in granules was seen in the dermal layers nearest the epidermis. He emphasizes that there is no increase in the number of mast cells near the blood vessels. He argues from his findings that the chromotrope substance in the epithelial layers has been supplied by the mast cells.

Whether this last conclusion is correct or not, Sylven's description of a relationship between mast cells and epithelial regeneration agrees with our findings in skin treated with a carcinogen, except that in the latter condition the mast cell reaction is much more intense. This accords with the conception that a chemical carcinogen elicits a specific trauma, followed by excessive regeneration (9).

Since it is now widely held that the tissue mast cells are not derived from the basophilic leucocytes of the blood, and since we have been unable to find any evidence in our observations of such an origin, the question arises how the mast cells manage to form their metachromatic granules within the connective tissue in which they lie. This can be accounted for satisfactorily by the fact that the "ground substance" of proliferating connective tissue described by S. H. Bensley (1) has been found to contain sulphuric acid esters of polysaccharides, and that the mast cell granules have the same general chemical structure. Another representative of this group of sulphuric acid esters of polysaccharides was isolated by Kabat (19), who identified the polysaccharide as a new substance of high molecular weight and named it hyaluronic acid. This acid has been found in the skin of pigs and rabbits. There is, therefore, a group of substances chemically closely related as sulphuric acid esters of high molecular polysaccharides, which are present in the connective tissue as the extracellular ground substance, while intracellularly they are represented by the metachromatic granules of the mast cells. The metachromatic staining is common to all members of this group that are polysulphuric acid esters, while mono-sulphuric acid esters do not share this property. There is thus a close chemical relationship between some constituents of the "ground substance" of connective tissue and the chromotrope substance present in the mast cells and possessing a heparin-like action.

Information on the biological effects of heparin other than its well-known inhibition of blood coagulation is meager. Highly relevant for the interpretation of our results are the observations of two workers, Fischer (14) and Zakrzewski (34), who demonstrated a growth-inhibiting effect on the *in vitro* growth of both normal and malignant cells. Fischer found that a concentration of 0.05 per cent of heparin was sufficient to inhibit growth. Fischer found also that heparin combines with proteins near their isoelectric point.

Relevant also is a brief consideration of ferments present in certain tissues such as testis and the skin. Discovered by Duran-Reynals (12) and called by him

"spreading factors," they are capable of hydrolyzing those sulphuric acid esters of the "ground substance" in which the acid is combined with the polysaccharide, hyaluronic acid. As the result of such an action the permeability of the connective tissue is increased. It is conceivable that the transportation of chromotrope substance by the mast cells to points where the activity of these spreading factors is increased is a means of restoring to normal the increased permeability of the connective tissue at these points. It is noteworthy that these ferments are found also in malignant neoplasms arising from those tissues in which they are normally present, and that in many of these neoplasms they are found in increased amounts (5). This has led to the suggestion that this ferment is a means by which a malignant tumor invades the connective tissue. The two possible functions in the process of skin carcinogenesis that can be attributed to the chromotrope substance carried by the mast cells—an inhibition of growth or a restoration to normal of the increased permeability of the connective tissue—are not mutually exclusive. On the contrary either of them, if conclusively demonstrated, would attribute to the mast cell reaction a defensive role in the development of skin cancer. This agrees with our findings that the mast cell reaction is well developed in resistant mice exhibiting a moderate degree of epidermal hyperplasia.

In the light of our observations the mast cell reaction can now be accepted as a fairly regular phenomenon encountered in the process of carcinogenesis induced by potent chemical carcinogens, and as an effect not peculiar to methylcholanthrene. Since its degree is correlated with the degree of nonneoplastic epithelial hyperplasia and is limited to the hyperplastic areas, but is independent of the number of applications of the carcinogen, one may conclude that the carcinogen is not directly responsible for the mast cell reaction. Nor is the reaction restricted to the Swiss strain of mice; it occurs also in the skin of another strain, the New Buffalo strain, which has been used extensively in this laboratory for the study of experimental skin carcinogenesis by methylcholanthrene.

SUMMARY AND CONCLUSIONS

The reaction of the mast cells has been studied in mouse skin during the various stages of carcinogenesis induced by minimal total doses of methylcholanthrene administered by a few applications given at long intervals of time to a large skin area. Under these conditions carcinomas develop as a rule in about 50 per cent of the animals, and long after the application of the carcinogen has ceased. Under these conditions carcinogenesis is accompanied by a pronounced increase of the mast cells in the dermis.

Our observations have established a number of relationships between the carcinogenic process and the reaction of the mast cells:

1. The mast cells increase in number long before the development of carcinoma, as a reaction related to the development of an epidermal hyperplasia and apparently conditioned by it.

2. This reaction, which is patchy rather than homogenous, increases with the degree of hyperplasia in the epidermis. It is most evident underneath those parts of the epidermis that have reacted with hyperplasia, and roughly in proportion to the degree of this hyperplasia. In the carcinoma itself mast cells are infrequent and may be completely absent in large parts of the growth, though there are massive accumulations in the immediate neighborhood of the tumor, especially where the contiguous epidermis shows advanced hyperplasia.

3. In the most advanced stages of the mast cell reaction the cells taking part in it exhibit considerable differences in their morphological and histochemical appearances. These differences are interpreted as indicating a greatly increased functional activity of the cells. One striking manifestation of such a difference is the golden-brown fluorescence in ultraviolet light acquired by some of the mast cells.

4. A significant feature of the mast cell reaction induced by chemical carcinogens is the contrast between its massiveness in the stages preceding the development of a carcinoma and its absence in the fully developed carcinoma, where epithelial growth processes are greatly enhanced.

5. The mast cell reaction is intense also in the skin of those resistant mice in which a slight degree of epithelial hyperplasia, induced in response to the carcinogen, has been arrested so as to delay or prevent its progress to the development of neoplasia. The mast cell reaction in such resistant mice is much more intense than in the most susceptible animals; *i. e.*, mice in which cancer develops after an exceptionally short period of induction. In the few susceptible mice that have so far come under our observation the reaction was in fact relatively weak.

6. These observations suggest that the mast cell reaction is associated with a defensive process against the development of skin cancer.

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Transplantable Methylcholanthrene Skin Carcinomas of Mice

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Three lines of transplantable skin carcinomas of mice induced by methylcholanthrene have been established in order to furnish material for a study of diurnal mitotic rhythm in carcinoma, which is being carried on by the staff of The Barnard Free Skin and Cancer Hospital under the direction of Dr. E. V. Cowdry. These tumors are free from the secondary infection that is often present in carcinomas produced on the surface of the skin by methylcholanthrene and, therefore, are more suitable not only for studies on cell division but also for chemical analyses, such as that of Carruthers and Suntzeff (1, 7) on the role of calcium and potassium in epidermal carcinogenesis. Skin tumors induced by tar have been successfully transplanted by a number of workers; Yamagiwa and Saigusa (8); Itô (3); Cramer (2); Mottram (5); and Kettle (4), but most attempts to transplant those elicited by the synthetic carcinogens have failed. After several unsuccessful attempts to transplant skin tumors produced by benzpyrene in mice, Salaman (6) was able to establish several lines of squamous cell carcinoma, which, however, were carried through only 3, 4, or 5 passages.

We have been able to establish 2 lines of squamous cell carcinoma, originally induced by methylcholanthrene, which have been carried through 20 and 21 passages respectively, and are still being maintained in this laboratory, and a third line, which was carried through 15 passages before it was lost.

MATERIALS AND METHODS

Two female Swiss mice were painted with a 0.3 per cent solution of methylcholanthrene in acetone 3 times weekly for 98 days, or approximately 14 weeks. The carcinogen was applied by a single stroke of a No. 3 camel's hair brush down the middle of the back. Another female Swiss mouse was similarly painted with a 0.3 per cent solution of methylcholanthrene in benzene 3 times weekly for 76 days, or approximately 11 weeks. In from 3 to 18 days following the last application of the carcinogen all 3 mice had developed squamous cell carcinomas in the treated area. Grafts of these tumors were introduced subcutaneously, under sterile conditions, into Swiss mice with a hypodermic needle, 2 mm. in diameter and 50 mm. in length, fitted with a metal plunger; thus the pieces inoculated were less than 2 mm. in diameter. In from 5 to 10 weeks, when these first grafts had grown until they were 1 to 1.5 cm. in diameter, they were again transplanted subcutaneously into other groups of Swiss mice. At irregular intervals, varying from approximately 20 to 60 days, transfer was made into new groups of Swiss mice.

A portion of each tumor was fixed in Bouin's fluid at the time of transplantation and paraffin sections were prepared, so that cellular changes in the tumor during its passage from one group of mice to another should not pass unnoticed.

By means of calipers 2 diameters at right angles to each other were measured on every tumor, at approximately two-week intervals. Thus, a rough indication of the rate of growth was acquired.

The Swiss mice used in these experiments were originally obtained from Tumblebrook Farms, Brant Lake, New York, and were subsequently pen-bred in our own laboratory. They were kept in a room in which the temperature was maintained at 78° F. by thermostatic control, and were fed Rockland Farms mouse pellets.

RESULTS

Tumor I was a squamous cell carcinoma that had been produced originally on the back of a female Swiss mouse by the application of a 0.3 per cent solution of methylcholanthrene in acetone 3 times weekly for 98 days, or approximately 14 weeks. The tumor was transplanted into 5 Swiss mice, in 2 of which it grew. After 35 days one of these subcutaneous tumors was inoculated under the skin of 11 Swiss mice, in 9 of which the inoculum grew. This growth has been transferred through 21 passages during a 2½ year period, at intervals varying from 22 to 97 days. The number of passages, the number of animals used in each passage, the number and percentage of successful inoculations, the intervals between passages, and the diameters of each tumor at each passage, are shown

in Table I. The percentage of successful inoculations has varied at different passages from 25 to 100 per cent, with an average of 68.5 per cent.

Tumor I was a well differentiated squamous cell carcinoma made up of large, clear cells with large vesicular nuclei, and was notably keratotic. Mitotic figures were numerous; the connective tissue stroma was not very dense. This tumor changed somewhat in microscopic appearance during passage from one group of animals to another, over the 2½ year period that it has been carried, becoming more undifferentiated and showing less tendency to keratinize. Fig. 1 shows a section taken from the original tumor, and

TABLE I: TUMOR I

No. of passage	No. of animals	No. of takes	Percentage of takes	Interval between passages, days	Dimensions at time of transplantation, mm.
1	5	2	40.0	35	18 × 13
2	11	9	81.8	24	9 × 7
3	11	10	90.9	34	24 × 15
4	5	3	60.0	22	12 × 11
5	18	12	66.7	63	
6	12	4	33.3	97	20 × 10
7	9	5	55.6	48	13 × 14
8	8	4	50.0	60	8 × 7
9	3	3	100.0	51	20 × 16
10	7	6	85.7	30	9 × 7
11	5	2	40.0	37	12 × 10
12	9	9	100.00	31	20 × 24
13	3	3	100.00	35	16 × 20
14	22	20	90.9	34	8 × 12
15	5	4	80.0	34	16 × 17
16	8	5	62.5	30	12 × 15
17	6	3	50.0	51	10 × 10
18	12	7	58.3	36	17 × 13
19	8	2	25.0	42	20 × 19
20	15	15	100.0	44	16 × 15
21	15	10	66.7		
		Average	68.5		

Fig. 2 a section removed at the 20th subcutaneous passage. Occasionally one of the transplants was allowed to grow subcutaneously for a period of 2 or 3 months. It would become quite large, attaining a diameter of more than 2 cm., and often invade the peritoneal cavity, but no evidence of lung or lymph node metastases was ever found.

Tumor II was also a squamous cell carcinoma from the back of a female Swiss mouse that had been painted 3 times weekly with a 0.3 per cent solution of methylcholanthrene in acetone for 98 days, or approximately 14 weeks. Pieces were transplanted subcutaneously into 4 Swiss mice, in 2 of which the tumor grew. After 42 days one of these tumors was again transplanted into 5 Swiss mice, in 4 of which successful inoculations were secured. This tumor has been carried through 20 passages in the past 2½ years at intervals varying from 26 to 108 days. Table II shows the number of passages, the number of animals used in each passage, the number and percentage of successful inoculations, the interval between passages, and the diameters of each tumor at each passage. With this tumor the percentage of successful inoculations varied between 12.5 and 80 per cent, with an average of 39.3 per cent. The number of successful inoculations was thus not so high as with tumor I. At no time has this tumor grown in all animals inoculated, whereas tumor I was successfully inoculated in 100 per cent of the animals at 4 different passages. Tumor II also grew somewhat more slowly than tumor I.

TABLE II: TUMOR II

No. of passage	No. of animals	No. of takes	Percentage of takes	Interval between passages, days	Dimensions at time of transplantation, mm.
1	4	2	50.0	42	16 × 13
2	5	4	80.0	30	
3	10	4	40.0	33	13 × 15
4	16	12	75.0	26	10 × 8
5	14	4	28.6	68	
6	11	4	36.4	63	
7	10	3	30.0	26	11 × 7
8	8	4	50.0	43	16 × 13
9	8	4	50.0	59	40 × 25
10	7	3	42.9	46	11 × 12
11	6	1	16.7	36	12 × 10
12	8	1	12.5	37	10 × 8
13	8	5	62.5	31	11 × 15
14	5	2	40.0	35	15 × 18
15	4	2	50.0	108	28 × 28
16	7	2	28.6	35	17 × 21
17	6	2	33.3	52	11 × 11
18	12	3	25.0	39	25 × 21
19	14	3	21.4	50	23 × 24
20	15	2	13.3		
		Average	39.3		

Microscopically, tumor II is a well differentiated squamous cell carcinoma. Its cells are large, clear, with enlarged vesicular nuclei, and mitotic figures are numerous. A well developed connective tissue stroma is present. This tumor has more of a tendency to keratinize than tumor I. In contrast to tumor I, its microscopic appearance remained fairly constant from passage to passage. Fig. 3 shows a section of the original tumor, and Fig. 4 a section removed at the 18th passage.

Tumor III, the third squamous cell carcinoma, arose on the back of a female Swiss mouse that had been painted 3 times weekly with a 0.3 per cent solution of methylcholanthrene in benzene for 76 days, or approximately 11 weeks. Portions were transplanted subcutaneously into 13 Swiss mice, and, after an interval of 70 days, from one of these mice into 12 more Swiss mice. In 11 of the 12 the tumor grew,

and subsequently was passed through 15 groups of mice at intervals varying from 23 to 82 days. It was then lost, probably because too few animals were used in the last passages. Table III shows the number of passages, the number of animals used at each passage, the number and percentage of successful inoculations, the intervals between passages, and the diameters of each tumor at each passage. The percentage of successful inoculations varied from 37.5 to 100, with an average of 66.2; greater than for tumor II, but almost the same as that for tumor I. This carcinoma, however, grew somewhat more slowly than the other two.

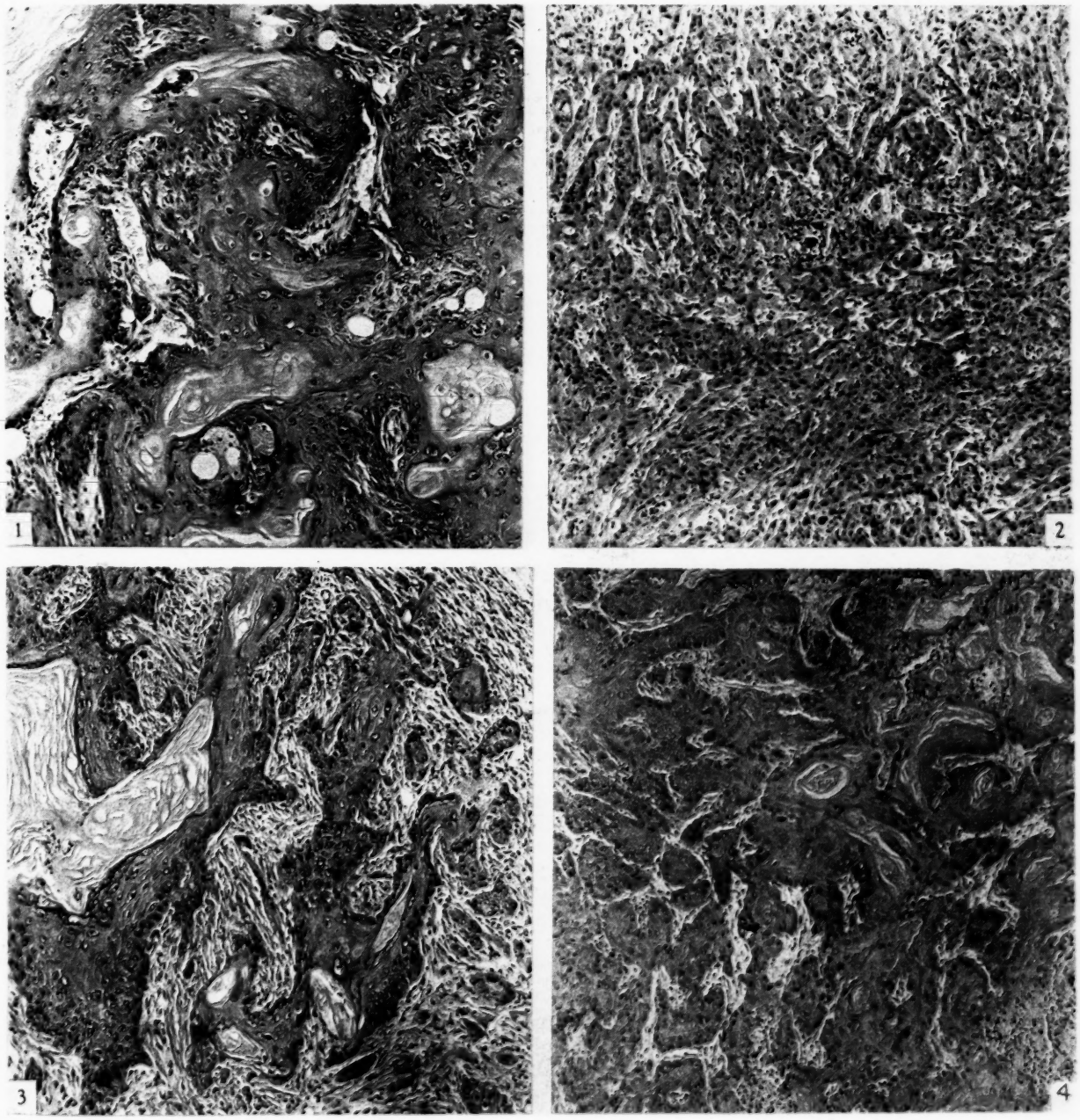

FIG. 1.—Tumor I. Original tumor produced on the skin of the back of a Swiss mouse by the application of a 0.3 per cent solution of methylcholanthrene in acetone. Mag. × 88.8.

FIG. 2.—Tumor I. Twentieth passage. Mag. × 88.8.

FIG. 3.—Tumor II. Original tumor produced on the skin of the back of a Swiss mouse by the application of a 0.3 per cent solution of methylcholanthrene in acetone. Mag. × 88.8.

FIG. 4.—Tumor II. Eighteenth passage. Mag. × 88.8.

Tumor III was also a squamous cell carcinoma. Originally it was more differentiated and showed less tendency to keratinize than either tumor I or tumor II. Its cells were smaller and more basophilic than those

of the other two growths, mitotic figures were numerous, and the connective tissue stroma was more dense than that of either of the other tumors. Like tumor II, the microscopic appearance remained relatively unchanged from passage to passage. Fig. 5 shows the original tumor, and Fig. 6 its appearance at the 14th subcutaneous passage.

SUMMARY

Three lines of transplantable methylcholanthrene skin carcinomas of mice have been established. Tumor I, originally a well differentiated, keratinizing, squamous cell carcinoma, has been carried through 21 subcutaneous passages over a period of 2½ years. During passage its microscopic appearance has changed, and it is now an undifferentiated, nonkeratinizing, squamous cell carcinoma. The average percentage of successful inoculations is 68.5, the highest for the 3 lines.

Tumor II has been carried through 20 subcutaneous passages. It is a highly differentiated, keratinizing, squamous cell carcinoma whose microscopic appearance has not undergone any significant change. It grows somewhat more slowly and has a lower percentage of successful inoculations (39.3) than tumor I.

Tumor III was carried through 15 subcutaneous passages and then was lost. It was originally more differentiated and showed less tendency to keratinize than either tumor I or tumor II. Like tumor II, its microscopic appearance remained relatively unchanged. The average percentage of successful inoculations (66.2) was higher than that of tumor II, but almost the same as that for tumor I.

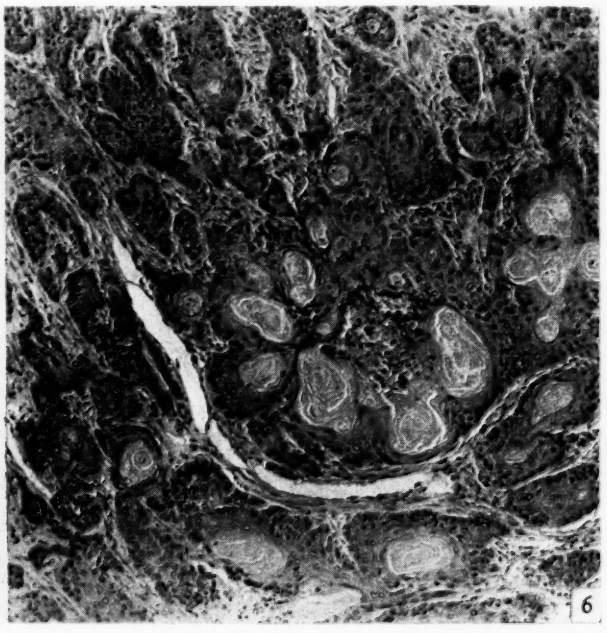

FIG. 5.—Tumor III. Original tumor produced on the skin of the back of a Swiss mouse by the application of a 0.3 per cent solution of methylcholanthrene in benzene. Mag. × 88.8.

FIG. 6.—Tumor III. Fourteenth passage. Mag. × 88.8.

TABLE III: TUMOR III

No. of passage	No. of animals	No. of takes	Percentage of takes	Interval between passages, days	Dimensions at time of transplantation, mm.
1	13			70	
2	12	11	91.7	30	
3	8	8	100.0	33	12 × 10
4	8	3	37.5	82	
5	11	11	100.0	63	12 × 10
6	8	6	75.0	58	8 × 9
7	6	4	66.7	23	9 × 7
8	12	8	66.7	29	8 × 10
9	8	3	37.5	31	12 × 14
10	8	6	75.0	51	16 × 17
11	15	8	53.3	32	20 × 15
12	6	5	83.3	37	13 × 7
13	5	5	100.0	31	13 × 15
14	5	2	40.0	55	14 × 18
15	8	0			
		Average	66.2		

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The Effect of Castration, Theelin, and Testosterone on the Incidence of Leukemia in a Rockefeller Institute Strain of Mice*

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The pronounced difference in susceptibility to leukemia between the sexes has as yet received no satisfactory explanation. In man, with the several types of the disease, 60 to 79 per cent of the cases are in males (1, 6, 7). In the majority of strains of mice showing a high leukemia incidence the ratio of susceptibility is the reverse, with the females showing an incidence often a third higher than the males. In considering an explanation there is a possibility that one sex may be more susceptible to the effect of inciting agents that are supposed to play some role in initiating the disease process. In support of this idea there is some evidence that the blood-forming tissues of men are more receptive than those of women to the stimulating effect of benzol (5). It seems more likely, however, that the differences in the incidence of leukemia between the sexes is in some way influenced by the endocrine system. The following investigation was undertaken to test this possibility.

MATERIALS AND METHODS

The mice used in the tests were from the highly inbred Rockefeller Institute Leukemia Strain (R.I.L.).[1] At approximately 4 weeks of age the females were divided into 3 groups, with litter mates in each group when possible. The animals in one group were ovariectomized and a 3 mgm. pellet of testosterone propionate [2] was implanted subcutaneously. A second group was ovariectomized but no treatment was given, and the third group was kept intact as a control.

The males were similarly divided into 3 groups, and at approximately 4 weeks of age the animals in one group were castrated and given a 2 mgm. pellet of theelin;[3] those of another group were castrated but given no treatment; while the third group was kept intact as a control.

The disease, after it develops, runs a fairly acute course and is characterized by considerable enlargement of the lymph nodes and extensive involvement of the thymus. The liver may be infiltrated, but the number of circulating white blood cells does not reflect the severity of the tissue involvement.

EXPERIMENTS

Females.—The 93 female mice in this test were divided as follows: 31 were ovariectomized, 36 were ovariectomized and each given subcutaneously a pellet of testosterone propionate approximately 3 mgm. in weight, and 26 of the group were normal, untreated controls.

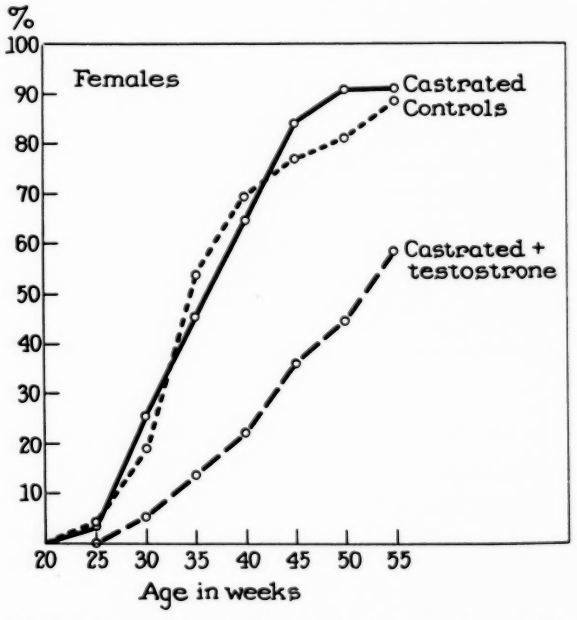

FIG. 1.—The points on the curves represent the number of mice that had developed leukemia by the age indicated, expressed as a percentage of the initial number of animals.

The results of this experiment are given in Fig. 1. The curves are based on the cumulative percentage of leukemia estimated at 5 week intervals. The disease does not appear before the 20th week of age, and in the controls and ovariectomized mice the rate increases rapidly thereafter. There is little difference between

* This investigation was aided by a fund for leukemia studies, contributed anonymously.

[1] The origin and analysis of this strain will be reported later by Dr. C. J. Lynch.

[2] We are indebted to the Schering Corporation for this product.

[3] Acknowledgment is made to Parke, Davis and Company for this product.

these 2 groups, as shown by the form of the curves on the time of development or the total incidence of leukemia. The curve for the castrated females treated with testosterone propionate is distinctly different. The disease not only appeared at a later age period, but only 58.3 per cent of the mice developed leukemia, which contrasts with 88.4 per cent and 90.3 per cent respectively for the controls and the untreated castrated animals. The later onset of the disease in the treated castrates is shown by the fact that the average age at death from leukemia was 299 days, while the other 2 groups averaged 248 days and 253 days.

Males.—Of the 99 male mice in this group 34 were castrated, 37 were castrated and given subcutaneously a pellet of theelin weighing approximately 3 mgm., and 28 were untreated to serve as controls.

The results, as shown in Fig. 2, demonstrate a sharp contrast between the castrated and control males. The 97 per cent incidence of leukemia for the former is the highest so far encountered in any group from the strain, and this is significantly different from the 53.5 per cent for the controls. The average ages at death from leukemia, 260 days for the castrated as compared to 300 days for the controls, indicate the later onset of the disease in the latter. The toxic effect of theelin was so great that it caused the death of the majority of the treated mice before or in the early leukemia age period. It is considered that the figures for this group have no significance, but it is interesting to note that between the 20th and 30th weeks of age the rate was definitely higher than in the controls, and even a little higher than in the castrated males.

For comparison the results with the 4 important groups from the foregoing experiments have been brought together. It will be noted in Fig. 3 that the curve for castrated males is almost identical with that for the female controls, and there is the same agreement between the male controls and the castrated females treated with testosterone propionate. The data in Table I further emphasize these similarities. The total incidence of leukemia for castrated male mice is 97 per cent, with 260 days as the average age at death from leukemia; and these figures closely approximate those for the control females, which had an incidence of 88.4 per cent and an average age at death of 253 days. The incidence and survival period for the intact males closely approximate the figures for the ovariectomized female mice treated with testosterone.

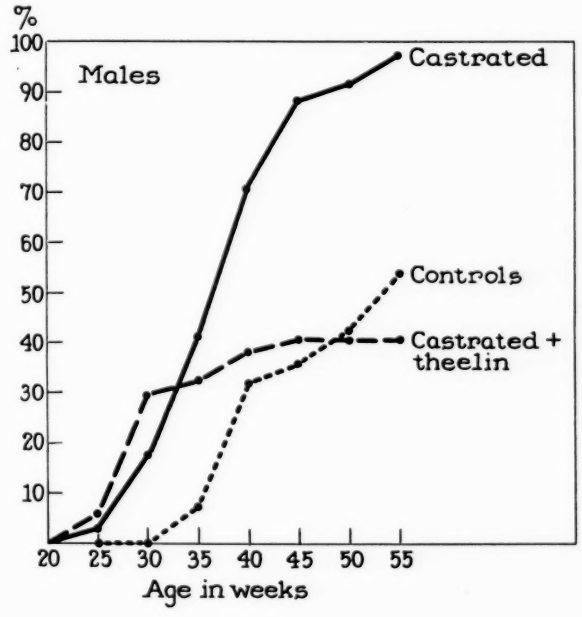

FIG. 2

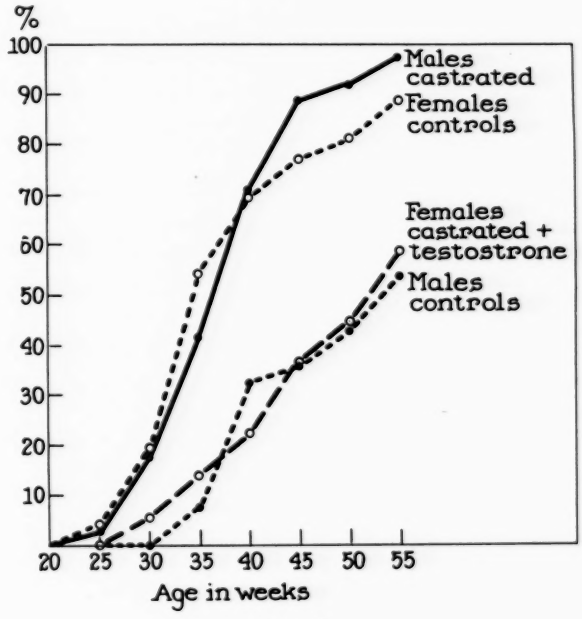

FIG. 3

FIGS. 2 and 3.—These figures are on the same basis as those above.

TABLE I

	Number	Average age at death from leukemia, days	Leukemia rate, %
Control females	26	253	88.4
Castrated males	34	260	97.0
Control males	28	300	53.5
Testosterone-treated, castrated females	36	299	58.3

DISCUSSION

Judged by the results of the present study the difference in leukemia incidence between male and female mice of the R.I.L. strain appears to be the result of some inhibitory action exerted by the male sex hormone, rather than a stimulation from the

ovarian secretion. This conclusion is based on the fact that the leukemia rate in ovariectomized and intact females is almost identical, and these figures are somewhat exceeded by the rate for castrated males. On the other hand, ovariectomized females treated with testosterone propionate have a rate significantly lower than the 3 groups above, and this closely approximates the rate for intact males. Gardner (2) and Lacassagne (4) have reported that the incidence of leukemia is increased in some stocks of mice by prolonged treatment with estrogenic hormones. More recently Gardner, Dougherty, and Williams (3) have reported that estrogenic hormones increase the incidence of lymphoid tumors in some strains but not in others. It is of interest to note that there is no constant sex difference in the rate of occurrence of lymphoid tumors in mice. In the present test of the effect of theelin on castrated males of the R.I.L. stock the incidence of leukemia in mice under 30 weeks of age was as high as that in the intact females and the untreated castrated males. Too few animals survived the toxic effect of the hormone to give data of any value for the later age periods. However it seems unlikely that estrogens would increase the rate above that noted in the untreated castrated males (97 per cent).

While the reported results indicate some inhibitory action of the male sex hormone, with the known interrelation between the endocrines this cannot be accepted as necessarily a direct effect on the lymphoid tissue. No attempt is made to correlate the present findings with our observations on the role of the adrenals in susceptibility to a transplanted leukemia of rats (8, 9).

SUMMARY

The spontaneous leukemia rate in the females of the Rockefeller Institute Leukemia Strain of mice is consistently higher than in the males. In the present experiments the incidence in ovariectomized females was 90.3 per cent, in intact females 88.4 per cent, and in castrated males 97 per cent. These figures are significantly different from the incidence in intact males, 53.5 per cent, and in ovariectomized females treated with testosterone propionate, with a rate of 58.3 per cent. On the basis of these findings it is suggested that the sex difference in susceptibility in the mouse strain under observation is due to an inhibitory effect of the male sex hormone rather than to a stimulation of the ovarian secretion.

So many of the castrated males treated with theelin died before or in the early leukemia age period that not a sufficient number were left to give significant figures on the leukemia incidence in this group.

Note: Since this paper went to press the following article has appeared: McEndy, D. P., Boon, M. C., and Furth, J. On the Role of Thymus, Spleen, and Gonads in the Development of Leukemia in a High-Leukemia Stock of Mice. *Cancer Research,* **4**:377-383. 1944. It is reported that in the Ak stock of mice the incidence of leukemia in mice ovariectomized at 23 to 56 days of age was 45 per cent, as compared to 74 per cent for the controls. Among males subjected to orchidectomy at 20 to 56 days the incidence of leukemia was 60 per cent, as compared with 52 per cent among the controls. The results with this stock appear to differ materially from those with the R. I. L. mice. This may be due to the ages at which the gonads were removed. In our experiments the average age at removal was under 4 weeks. The authors mentioned above made no distinction between animals gonadectomized before and after reaching maturity.

Acknowledgement is made of the technical assistance of Mr. Jerry Simunek.

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Decreased Mutual Adhesiveness, a Property of Cells from Squamous Cell Carcinomas*

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(Received for publication May 6, 1944)

In the course of microscopic observations on living cells from a lip carcinoma it was found that these cells could be separated one from another by needles with the greatest ease. When similar observations were made on normal lip epithelium the cells seemed to be far more strongly adherent, and were pulled apart only after considerable resistance had been overcome. This suggested the possibility that a decrease in adhesiveness might be characteristic of malignant cells. Malignancy consists essentially in local invasiveness and distant metastasis, both of which would be favored if malignant cells could break away readily from one another, but hampered if they were strongly adherent in sheets.

Accordingly, experiments were planned to measure quantitatively the forces necessary to separate carcinomatous squamous cells, as compared with normal squamous cells and squamous cells from benign tumors.

METHOD AND MATERIAL

The method used for measuring the adhesiveness of cells was a modification of that employed by Sichel (9) for determining the elasticity of muscle fibres, and by Norris (6) for measuring the surface tension of erythrocytes. This method, as adapted to the present problem, depends upon the amount of bend in a needle when it pulls apart a pair of cells.

Two glass microneedles were attached to a Chambers micromanipulator. One (the holding needle), stiff and blunt, served to hold one of an attached pair of cells firmly against a coverslip, and remained stationary. The second (the pulling needle), flexible and sharp-pointed, was inserted into the other cell of the pair and, on being moved by the micromanipulator, pulled the cells apart. As the cells resisted separation because of their mutual adhesion the pulling needle bent, and its bending reached a maximum just before the cells had been pulled apart. The maximum bend was measured, and the value thus obtained was expressed as the force necessary to separate the pair of cells.

The bend of the needle was found by subtracting the excursion of the tip from that of the shaft. For example, at maximal bending (just before the cells separated) it might be found that the shaft had been displaced 0.20 mm. by the micromanipulator, but that the tip had moved only 0.03 mm.; hence the bend of the needle was 0.17 mm.

The excursion of the needle tip was measured under a microscope provided with a filar micrometer eyepiece. The excursion of the shaft was measured as follows. To the shaft was attached a glass rod 25 cm. long, which served as a lever to amplify the movement of the shaft. The distal end of the rod was provided with a fine tip. This tip was focused by a microscope on a mirror, which reflected the image on a ground glass millimeter scale. On the scale, the excursion of the needle shaft was amplified about 50 times.

The microneedles were drawn from Pyrex glass rods having a uniform diameter of 0.85 mm. A Livingston microneedle puller (5) was used for this purpose. Each pulling needle was calibrated by hanging microweights on its tip in such a position that the force was applied in the same direction as it would act when the needle was pulling a pair of cells apart. The bend in the needle thus produced by hanging a weight on its tip was read on a filar micrometer attached to a horizontal microscope. By using a series of microweights a calibration curve was constructed for each pulling needle.

The microweights were cut from platinum wire of uniform diameter weighing 1 mgm. per 0.565 cm. Lengths of wire were measured and their weights calculated; they ranged from 0.25 mgm. to 2.00 mgm.

The cells to be examined were placed upon a coverslip in physiological salt solution, and the coverslip was then inverted over a moist chamber. It was not necessary to consider bending of the needle by surface forces since the force required to separate a pair of cells was great enough so that relatively stiff needles could be used.

* This investigation was aided by a grant from The International Cancer Research Foundation.

The calculations in a typical experiment were as follows:

Ocular micrometer reading of pulling-needle tip at start = 3.5
" " " " " " " " end = 6.0
" " spaces moved by tip of pulling needle = 2.5
2.5 × 0.012 mm. (micrometer factor) = movement of needle tip = 0.030 mm.
Scale reading of pulling-needle shaft at start = 30 mm.
" " " " " " " end = 40 mm.
" movement " " " " = 10 mm.
10 mm. ÷ 50 (amplification factor of lever) = movement of shaft of pulling needle = 0.200 mm.

0.200 mm. (movement of shaft of pulling needle)
0.030 " (" " tip of pulling needle)

0.170 " = bend in pulling needle

The calibration curve of this needle showed that it bent

0.2 mm. with 2 mgm.
0.1 " " 1 "
0.05 " " 0.5 "

Therefore, by interpolation, the force required to separate the pair of cells = 1.70 mgm.

Squamous epithelium obtained from scrapings of fresh tissues was used in these experiments. Scrapings were made from the normal lip and the cervix uteri, from squamous cell papillomas of the skin, and from squamous cell carcinomas of the lip and of the cervix. Much of this material was obtained from the Radiology Department of the Philadelphia General Hospital. Material was also obtained from the Surgical Department of the Lankenau Hospital. The tissues were scraped with a blunt-pointed instrument and the cells thus removed were placed on a coverslip in Gey's solution (3). In selecting cells for an experiment only those were used that were nonkeratinized and apparently viable. Since there did not appear to be any obvious differences in cell size in comparable series, and since there was no apparent correlation between cell size and adhesiveness, cell size was not considered in the calculation.

RESULTS

Qualitative differences between normal and carcinomatous cells.—Striking differences were observed between normal and carcinomatous cells from the lip when pairs of cells were pulled apart. In normal squamous cells, tension lines developed in the cytoplasm, the nuclei often became elongated, and the cells separated only after considerable distortion; when they finally parted the cells snapped back into approximately their original shape. These observations indicated that the cells were firmly adherent to one another. Similar observations on squamous epithelium are recorded by Chambers and Renyi (2). In contrast, the cells from squamous cell carcinoma of the lip appeared to separate with much less resistance, showing less distortion and less prominent tension lines. These observations are recorded in a series of photomicrographs (Figs. 1 to 6).

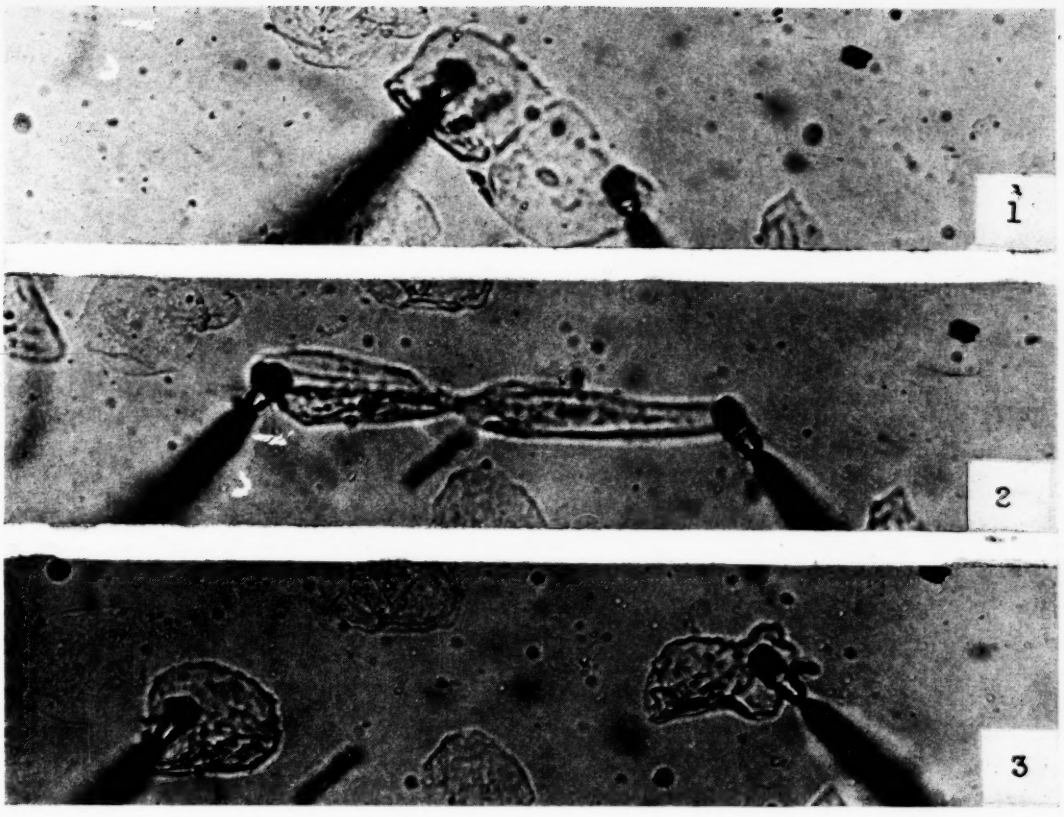
Quantitative differences.— The forces required to separate pairs of cells derived from normal and carcinomatous lips, normal and carcinomatous cervices, and skin papillomas were measured by the method described above. In each of these groups the cells were obtained from 5 individuals, and from each specimen 10 pairs of cells were examined, a total of 50 pairs of cells in each group. The results (Table I) are expressed as the mean number of milligrams (with the standard error of the mean) required to separate pairs of cells. Values for carcinoma of the lip and cervix are seen to be distinctly lower than those for normal cells of these organs and for skin papilloma. When carcinomatous and normal cells from the lip were thus compared an average of only 0.47 mgm. was required to separate pairs of carcinomatous cells, as compared with 1.42 mgm. to pull apart normal cells, a three-fold difference. An even greater contrast was found between cells from carcinoma of the cervix and from the normal cervix. Here the average force required to separate pairs of carcinomatous cells was 0.18 mgm., whereas for normal cells it took a force of 1.11 mgm., a difference of 6 times. It is interesting that the adhesiveness of skin papilloma cells ranks this lesion with normal epithelium rather than with malignant cells, the average for the papilloma cells being 1.25 mgm.

TABLE I: FORCES REQUIRED TO SEPARATE PAIRS OF CELLS BY MICROMANIPULATION

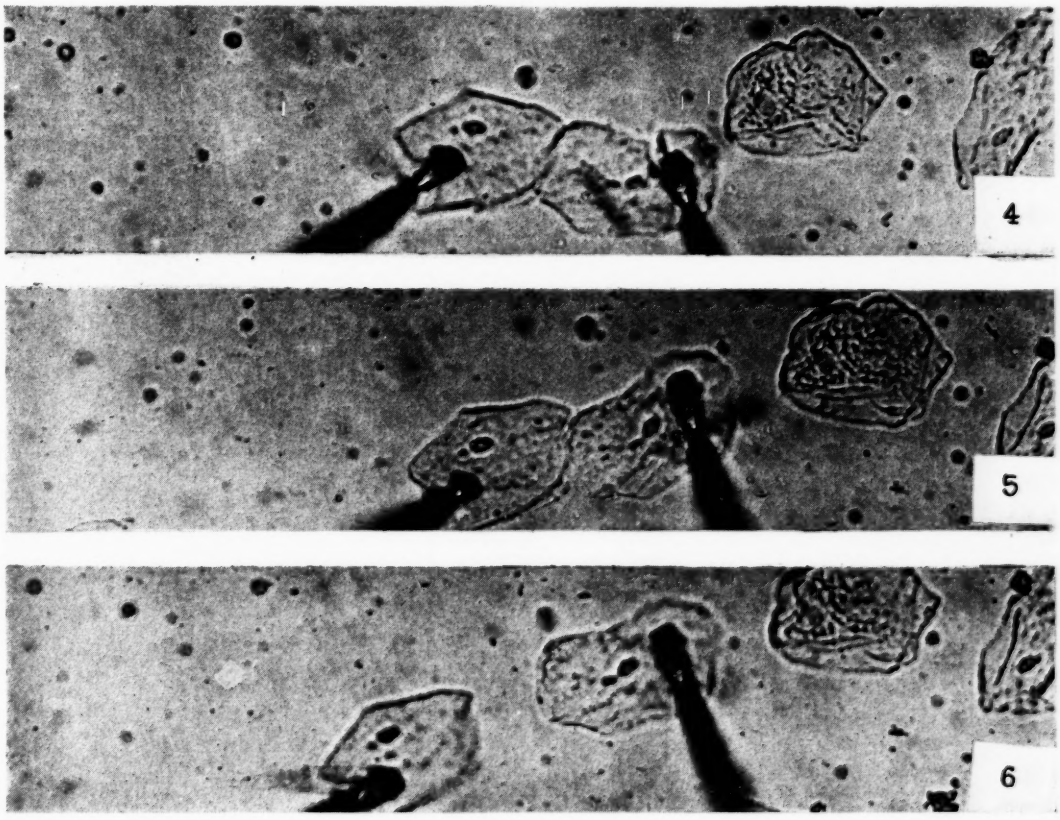
Derivation of cells	Mean and its standard error, mgm.
Normal lip	1.42 ± 0.041
Carcinoma, lip	0.47 ± 0.051
Papilloma, skin	1.25 ± 0.032
Normal cervix	1.11 ± 0.039
Carcinoma, cervix	0.18 ± 0.022

Each figure is based upon 50 pairs of cells and represents the mean (with its standard error) of the force in mgm. required to separate the cells by micromanipulation. It is seen that the values for carcinomatous cells are much lower than those for normal cells and for cells from papillomas.

The same results are represented graphically in Figs. 7 and 8, which show the distribution of values for adhesiveness. The distribution for carcinomatous and normal cells of the lip is represented in Fig. 7. Though there is slight overlapping carcinoma cells (black rectangles) lie mostly on the left side of the graph, indicating low values of adhesiveness, while normal cells (hatched rectangles) are mostly grouped on the right side of the figure, indicating their greater adhesiveness. Even more striking separation of malignant and normal cells is shown in Fig. 8, which represents the distribution of values for adhesiveness in cells from the cervix uteri. The malignant cells



FIGS. 1 to 3.—A pair of living squamous epithelial cells from a normal lip being separated from each other by microneedles. In FIG. 1 a needle has been placed in each cell. In FIG. 2 the needles have been moved apart, stretching the cells, which are thereby distorted. Tension lines appear in the cytoplasm as the cells cling to each other tenaciously. In FIG. 3 the cells have finally separated and have retracted into approximately their former shape. The needles are widely separated.



FIGS. 4 to 6.—A pair of living squamous epithelial cells from a carcinoma of the lip being separated from each other by microneedles. In FIG. 4 a needle tip has been placed in each cell. In FIG. 5 the needles have been moved only slightly apart and the cells begin to separate. Note the lack of distortion in these cells as compared to FIG. 2. In FIG. 6 the cells have been completely separated by only a slight additional movement of the needles. Notice that the needles in this whole series of manipulations have remained relatively close together as compared with the movements of the needles required to separate the normal cells in FIGS. 1 to 3. It is apparent that these carcinomatous cells were far less mutually adherent than the pair of normal cells.

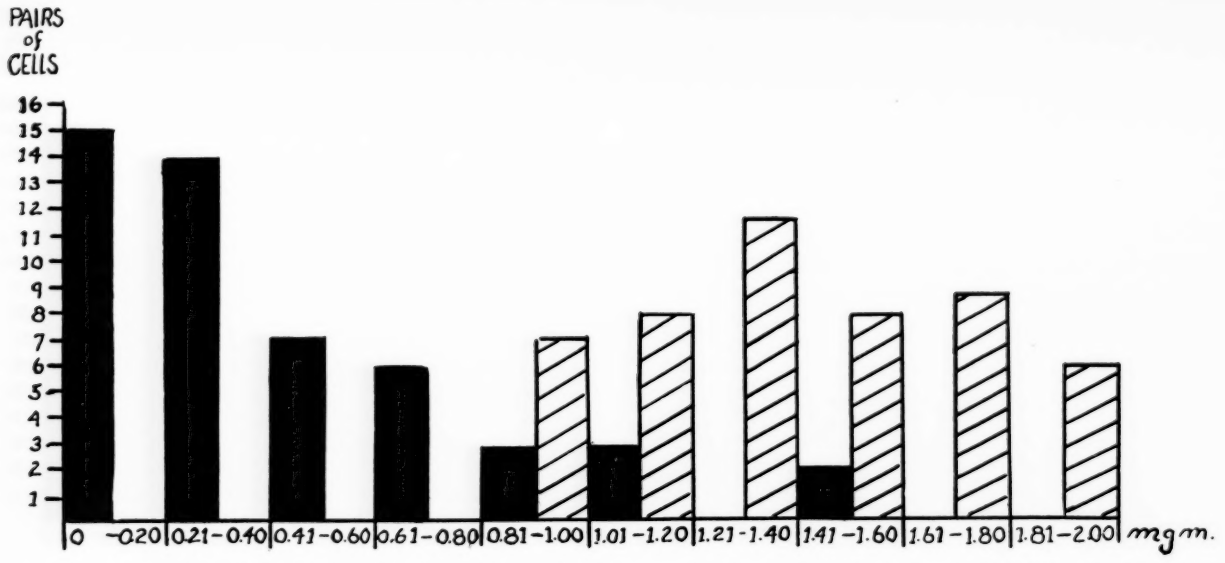


FIG. 7.—Distribution of the forces required to separate, by micromanipulation, pairs of squamous epithelial cells derived from the lip. The solid black columns represents cells from carcinomas of the lip, the crosshatched columns cells from normal lips. With few exceptions the carcinomatous cells are shown to be separable by distinctly smaller forces than are necessary to separate normal cells.

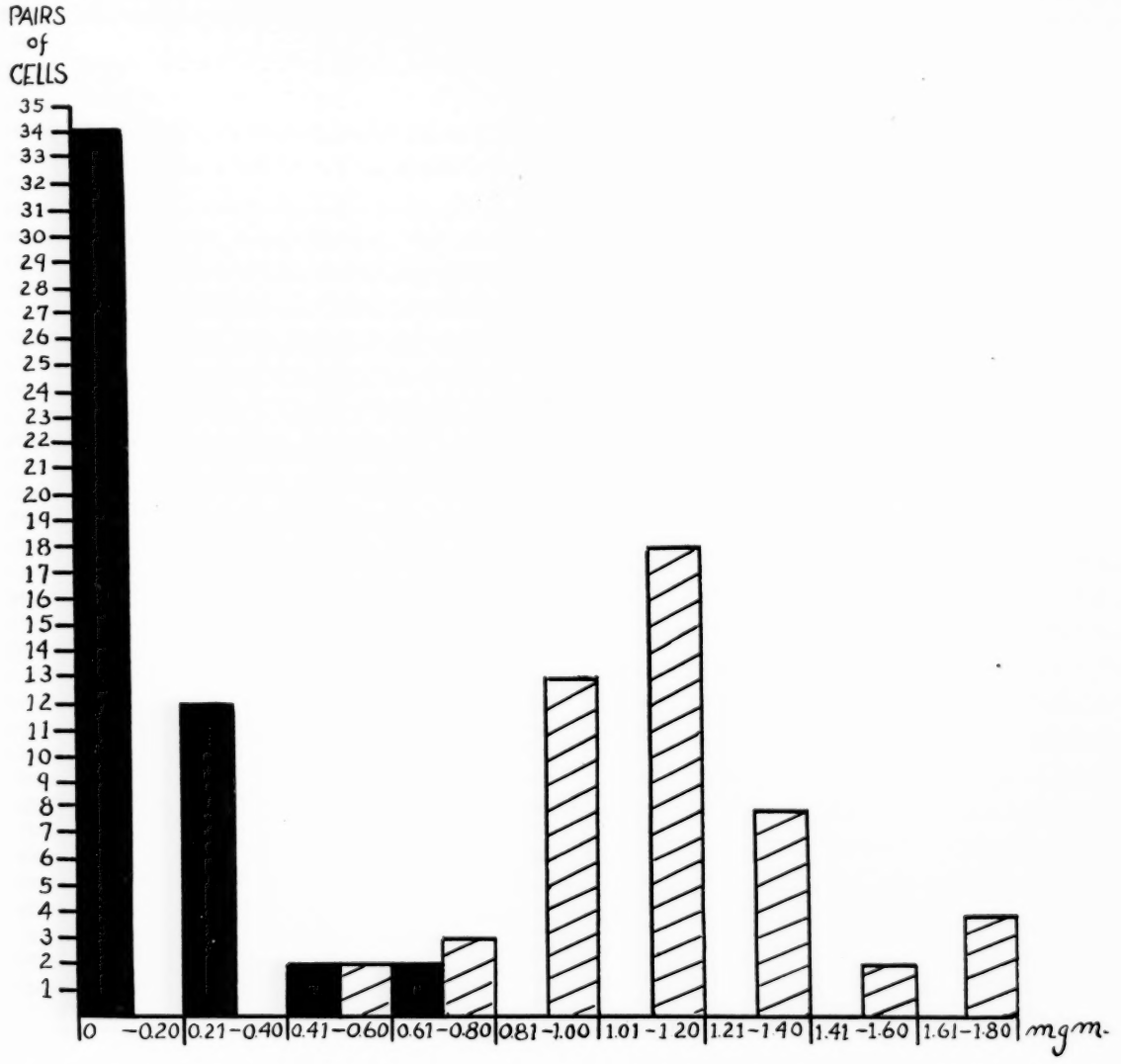


FIG. 8.—Distribution of the forces required to separate, by micromanipulation, pairs of squamous epithelial cells derived from the cervix uteri. The solid black columns represent cells from carcinomas of the cervix, the crosshatched columns, cells from normal cervices. With few exceptions the carcinomatous cells are shown to be separable by distinctly smaller forces than are necessary to separate normal cells.

are mostly grouped at the lowest values, indicating that they were pulled apart with hardly any resistance, in contrast with the much higher values obtained from normal cervical cells.

It is therefore concluded from these experiments that the assumption of malignancy by squamous epithelial cells of the lip and cervix uteri is accompanied by decrease in the adhesive forces that normally hold these cells together.

DISCUSSION

The decreased adhesiveness observed in carcinoma cells of the lip and cervix, as compared with that of normal cells, is of interest chiefly because of its possible bearing on the nature and mechanism of malignancy.

As long as squamous epithelium is held together firmly in sheets there is little likelihood of free penetration of the surrounding tissues, or of cells breaking into vessels and being transported to distant organs. On the other hand, should the adhesive forces that normally bind squamous epithelium together be greatly lessened, then presumably cells might break loose from one another and be free to move off by amoeboid motion into tissue spaces, lymphatics, and blood vessels. These conditions would favor both local invasiveness and distant metastasis.

Thus lessened adhesiveness in these carcinomatous cells suggests a physical basis for the property of malignancy.

In this connection, it is of interest to cite observations of Rous, Beard, and Kidd (7) on the relation of adhesiveness to metastasis. In their studies on the virus papilloma of rabbits they state that: "The virus-induced papillomas frequently penetrate into the blood and lymph vessels, but their cells adhere to one another, retaining the tenacious association that is so evident in the high, peaked surface growths. Instances of unaided metastasis formation have yet to be observed, but slight operative interferences are followed not infrequently by the development of secondary nodules in the lungs."

No attempt has been made in the present study to ascertain the cause of decreased adhesiveness in cells. However, it is well known (4) that decreased adhesiveness may be associated with lack of calcium in the fluid medium. Further, a remarkable decrease in calcium content has recently been found by Carruthers and Suntzeff (1) in chemically induced squamous cell carcinomas of mice. They found that the tissue calcium shows an initial drop soon after application of the carcinogen, and later a second drop when the cells become carcinomatous. Also, reduction in calcium and magnesium was demonstrated by Scott (8) in hyperkeratosis, warts, and in human breast and skin cancers. These observations suggest a possible chemical basis (decreased calcium content) for the lessened adhesiveness of cells from squamous cell carcinomas found in the present study.

SUMMARY AND CONCLUSIONS

1. The mutual adhesiveness of normal and of neoplastic squamous epithelial cells from the lip and from the cervix uteri was measured in milligrams by a method dependent upon the bend produced in a microneedle when a pair of cells was pulled apart.

2. Normal squamous epithelial cells from the lip and from the cervix were found to have relatively high values of adhesiveness.

3. Benign neoplastic squamous cells from skin papillomas had values of adhesiveness in the same range as did normal squamous cells.

4. Malignant neoplastic squamous cells from carcinomas of the lip and from carcinomas of the cervix showed mean values of adhesiveness far below that of the normal cells.

5. Decrease in mutual adhesiveness in cells from carcinoma of the lip and cervix uteri may constitute the physical basis for the malignancy of these cells. Such cells, no longer strongly adherent to each other in sheets, would presumably break loose and then be free to penetrate tissue spaces and vessels. Local invasiveness and distant metastasis would thus be promoted.

6. It is suggested that decreased mutual adhesiveness in cells of squamous cell carcinoma may be related to a lowered calcium content of these cells.

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The Mode of Origin of Tumors

Solitary Localized Squamous Cell Growths of the Skin*

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INTRODUCTION

The mode of origin of tumors, while clearly a matter of fundamental biological interest as well as of considerable practical importance, has been strangely neglected by most modern pathologists. Many text books fail to mention it, or touch on it but lightly and with no evidence to support the views expressed; and many pathologists appear to have no clear ideas on the subject. The most prevalent view is that each tumor has a simple unicentric origin, arising at a single point in time, from a single small focus of cells, and enlarging only by multiplication of these cells and their descendants. This strict unicentric view is largely a legacy from Cohnheim (5) who, nearly three-quarters of a century ago, raised "the question of the central or peripheral growth of a tumour; understanding by central growth one resulting from the multiplication of the tumour elements themselves, and by peripheral an enlargement of the tumour by a new formation proceeding from the tissues surrounding it." Acceptance of Cohnheim's hypothesis of embryonic rests of course precluded the possibility of peripheral growth. In his own words, "this distinction is meaningless if the tumours do not originate in the fully formed tissues of the part. . . . . For if, as we think, tumours develop from embryonic germs, a peripheral growth in the above sense does not take place."

Although Cohnheim's hypothesis of the origin of tumors from superfluous embryonic cells has been abandoned by most modern pathologists, who are now satisfied that, on the contrary, most tumors *do* "originate in the fully formed tissues of the part," his concept of restricted unicentric origin and purely intrinsic growth has largely persisted. The popularity of this view may be gauged from the following citations from well known works on tumor pathology.

Mallory (11) insisted that "Tumors grow entirely by multiplication of their own cells, not by transformation of normal cells into tumor cells"; and that attempts to trace gradations between normal and neoplastic tissues are "founded on incorrect observation, interpretation and deduction." According to McFarland, (12) "It seems well to think of a tumor as beginning at a minute focus, starting, as it were, from a single cell or group of cells, and increasing in size through multiplication of the particular elements concerned. . . . . There seems to be no ground for assuming continuous transformation of normal tissue into tumor—no successive beginnings." Kettle (9) said, "It is generally held that tumours arise from one cell or group of cells, and not as the result of a change affecting a comparatively large area. Whatever may be the size of the tumour, all its cells are the direct descendants of the mother cell or cells." MacCallum (10) does not discuss the general question of the mode of origin of tumors; but, while he observes of carcinoma of the skin that where the cancerous epithelium is in continuity with the surrounding epidermis there is not an abrupt transition, yet he says, "It is not believed that the epidermis is converted into tumor tissue as the tumor spreads, but that all tumor epithelium arises from that which first began to grow"; and he explains the gradual transition from epidermis to tumor as due to "a secondary healing together." Ewing (7), after briefly discussing the possibility that tumors may develop by progressive neoplastic change in a field of tissue, concludes, "yet these instances of lateral extension of tumor processes, if they eventually stand the test of criticism, are rare, and it should be emphasized that the great majority of tumor-cells are isolated in origin and throughout their history." In view of his own immediately preceding comments on the sequences of changes to be seen in the genesis of cancers of the breast, and his depiction in his Fig. 4 of "atypical epithelial hyperplasia on the edge of a beginning carcinoma of the skin," Ewing's retreat to the orthodox unicentric view appears illogical.

A few general pathologists, however, have dissented from the strict unicentric views and have held that at least some tumors arise from more or less extensive fields of tissue and enlarge not only by cellular proliferation but also by progressive neoplastic conversion of tissue within those fields. The following succinct statement by Borst (1) is worth citing at length. "Each tumor is at first locally limited; it starts from a field

* Because of the difficulties of international communication the author has not read proof of this article.

that usually is narrowly circumscribed, and at its periphery a histogenetic study is only possible if the tumor-formative field has not yet been totally incorporated in the growth, *i.e.,* in early beginning tumors, or if, as is seldom the case, further similar foci are present in the neighborhood of an already established tumor." After referring to the deceptive appearances that may be produced at the margins of carcinomas by irritative epithelial hyperplasia and the admixture and fusion of cancerous and noncancerous tissue, Borst goes on to say, "In examining the periphery of a carcinoma, then, one must be very cautious and critical. The view must be adhered to that the predisposition to carcinomatous change is generally restricted to a circumscribed focus; as long as this disposition is not yet wholly exhausted, the transition from normal to cancerous epithelium at the margin of a carcinoma can be traced; if, however, the whole of the predisposed focus has undergone cancerous change, then the established carcinoma grows purely intrinsically, and a continuous cancerous transformation of hitherto normal epithelium at the periphery of the carcinoma no longer occurs. This applies to the so-called unicentric carcinomas, which comprise the majority. Infrequently the formation of a carcinoma appears to be multicentric. Such cases merge into those with primary multiple development of carcinomas in an organ or system. And in yet rarer cases an organ appears to be predisposed throughout to the development of carcinoma, so that this commences simultaneously in very many places—diffuse origin of cancer, *e.g.,* in the stomach, kidney, liver. In the case of multicentric cancer formation in an organ, enlargement of a carcinoma by the peripheral addition of neighboring cancerous foci can take place."

In his *Treatise on Tumors* Hertzler (8) stated that evidence had accumulated to substantiate the view that carcinomas may enlarge by appositional growth and by the addition of multicentric foci. In intestinal growths, "the changes in the glands gradually shade off into the normal, as if some stimulus were causing successive glands to undergo abnormal proliferation, the changes being the less marked the further removed the glands are from the source of stimulation. The same is frequently seen in the skin epitheliomas." Yet Hertzler then falls back to the orthodox unicentric viewpoint.

That mammary tumors often arise simultaneously or successively from extensive tracts of breast tissue is clear from the work of many pathologists, notably Cheatle (3), Nicholson (16), Cheatle and Cutler (4), and Muir (1941). To Cheatle belongs the credit for first demonstrating this conclusively in sections of whole breasts, and for insisting that "the primary cancer process transforming epithelial into malignant cells may commonly operate on extensive duct surfaces. . . . . Having been established at one part of a duct, it may affect other parts of it, or other ducts." Nicholson, endorsing Cheatle's conclusions, said, "I have insisted for years that hyperplasia passes insensibly into carcinoma, and that this gradual change can nowhere be better studied than in the breast, and that tumour formation is here multi-, or rather omnicentric." Muir expresses the same conclusions as regards mammary cancer in the following words, "Malignancy is often not only of multicentric origin but can be seen to occur gradually and to affect groups of cells in a diffuse fashion, all stages of the process being traceable"; the neoplastic change "is regional rather than focal."

Elsewhere, in his *Textbook of Pathology,* Muir (15), after stating that, "As a rule, the origin of a malignant growth appears to be from a single focus," goes on to say, "While the cells of a malignant growth are generally sharply demarcated from those of the surrounding tissues, it may be impossible sometimes to say exactly where the margin of the growth is. This is especially so in the case of epithelioma, where there may be a gradual transition between the cells of the tumour and the adjacent epithelium. Whether this means that the adjacent cells are being stimulated to malignant proliferation by the tumour cells or whether the change in them occurs because they have been exposed to the same irritation, is a difficult question to answer."

Most notable of recent workers to insist on the field-origin of epidermal carcinomas are Brunschwig and Tschetter (2), who, in a study of early skin tumors, find "that the processes involve a segment of the epithelium and that they are not the result of changes arising in one cell or a small nidus of cells." They describe and depict the marginal zone of direct continuity between noncancerous epithelium and cancerous epithelium, which they hold is "best explained by the hypothesis of progressive cancerization of the normal epithelium at the margins of the initially altered segment." In early skin tumors produced in mice by applications of methylcholanthrene, Brunschwig and Tschetter also find and depict similar evidence of field-origin and progressive cancerization within the affected field.

Brunschwig and Tschetter were not the first, however, to reach these conclusions on experimental grounds. In 1923 Deelman (6) had made his careful studies of the mode of inception of tar cancers of the skin of mice; and had shown that these tumors arose in a field of tissue by progressive alteration of the epithelium of that field, commencing with hyperplasia, and passing gradually into papilloma formation, and this into carcinoma; and that the origin of these

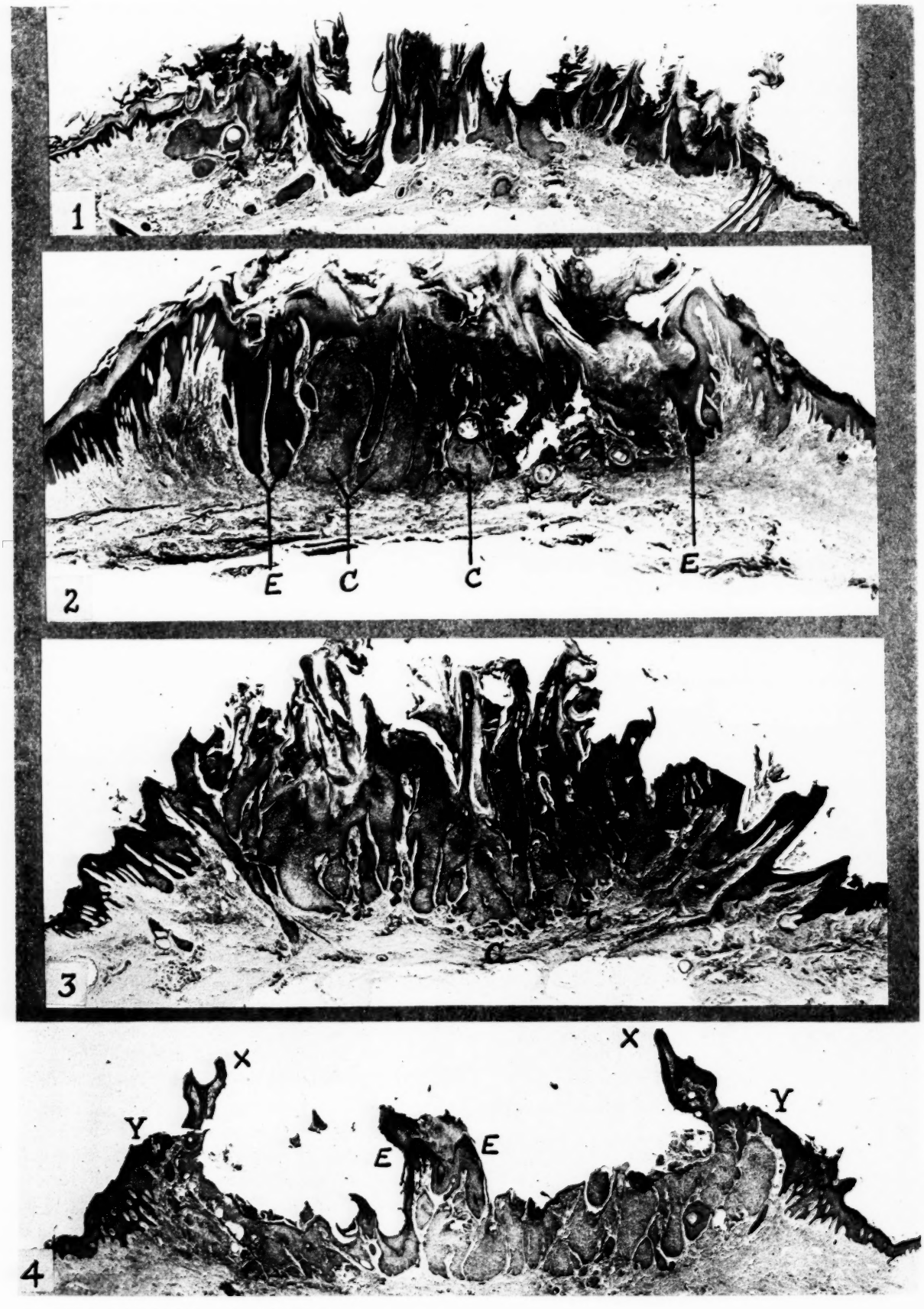

FIG. 1.—Case I. Vertical section. Mag. × 8.

FIG. 2.—Case II. EE, downgrowths with perfect epidermal structure. CC, atypical downgrowths. Mag. × 10.

FIG. 3.—Case III. CC, cancerous foci with anaplastic cells. Mag. × 9.

FIG. 4.—Case IV. XY, zone of transition between hyperplastic epidermis and crater lip X. EE, epithelium with perfect epidermal structure. Mag. × 8.

tumors was multicentric and multicellular. Similar field-origin is evident, though often not explicitly stated, in the observations of many subsequent workers in experimental carcinogenesis. Of these we may instance Orr (17), whose descriptions and figures of the inception of tumors in mouse skin following the application of carcinogenic hydrocarbons show clearly the widespread distribution of both the epidermal and dermal changes leading up to tumor formation. Mottram (13) is, I believe, the only experimentalist who has explicitly interpreted his results as pointing to the origin of experimentally produced tumors from single cells. His conclusion, however, is based on the assumption that excessive cellular multiplication takes place from the very commencement of tarring and produces a steadily increasing colony of proliferating cells from then onwards, an assumption not only opposed to our knowledge of precancerous changes in human tissues, but specifically refuted also by other experimentalists. Thus, of precancerous hyperplasia evoked by carcinogens, Orr says, "This epithelial increase . . . . is almost immediate, and attains its full extent within the first week, after which there is but little change until the time, about three months later, when tumours are going to arise."

We are faced, then, on the one hand by a large body of authoritative and widely accepted opinion, from Cohnheim to Ewing, that most tumors are strictly unifocal (and therefore unitemporal) in origin and that their growth is purely intrinsic; and on the other hand, by clear evidence, like that of Cheatle, Muir, Deelman, and Brunschwig and Tschetter, that this certainly does not obtain for at least some human and experimental tumors.

My own studies have convinced me that the strict unifocal view is false; and, in the light of this conviction, I decided to re-examine carefully my specimens of tumors of the human epidermis and related stratified epithelia: those of the lip, tongue, vulva, and penis. These epithelia were chosen for two reasons. In the first place because, since they are accessible to direct examination, the development of tumors in them is often closely observed from their inception and early tumors are often available for microscopical examination; and in the second place, because such tumors presumably afford a parallel to experimentally produced epidermal papillomas and carcinomas. Of my collection of nearly 500 epidermal tumors, about 150 afforded some relevant information as to their mode of origin, and of these 40 typical specimens were selected for detailed study. The present paper is concerned only with *solitary localized squamous cell growths of the skin,* of which 10 selected examples are described. Other varieties, namely extensive superficial epidermoid carcinomas, basal cell and allied carcinomas of the skin, and carcinomas of the lip and tongue may be described in a later paper. The selected tumors were sectioned vertically through the centre with as much as possible of the surrounding tissues. Paraffin-embedded sections were prepared and stained by hematoxylin and eosin, iron-hematoxylin and Van Gieson's stain, and by Verhoeff's stain for elastic tissue.

Case I. (section no. 4440)

A hemispherical growth 1.5 cm. in diameter, with a heavily keratinized, rough surface, was excised from the forearm of a man of 85. Most of the keratin became detached during preparation of the sections.

The epithelium is everywhere perfectly differentiated, with no cytological indications of its neoplastic qualities. That it is neoplastic and cancerous, however, is shown by its invasion and disruption of the dermis. As Fig. 1 shows, the surrounding epidermis undergoes gradual hyperplastic thickening and keratosis as it approaches the growth, and this hyperplastic epidermis passes gradually into papillary neoplastic epidermis, with no visible alterations in the cytology of the epithelium. The epidermis of the growth shows fully differentiated spinous cells, a prominent stratum granulosum, and a sharply demarcated stratum corneum. Mitoses are few, and little if at all more numerous in the neoplastic tissue than in the hyperplastic epidermis. Where hyperplasia ends and neoplasia begins, and where the latter is innocent and where malignant, it is impossible to say.

The dermis beneath the growth and the immediately neighboring epidermis shows an abundant infiltration by lymphocytes and plasma cells. The dermal elastic tissue shows definite increase and degeneration, appearing in hematoxylin-stained sections as a conspicuous pale blue layer measuring up to nearly 2 mm. thick and consisting of almost homogeneous material formed by the fusion of swollen elastic fibers. Except in the immediate proximity of the tumor, this altered elastica is unassociated with round cell infiltration; and it extends with a little diminution in thickness right to the edges of the section, about 1 cm. from the growth margins. It is interrupted by the epithelial downgrowths of the tumor, beneath which there is no sign of elastic overgrowth.

Case II. (section no. 5414)

A hemispherical, horny growth of 6 months' duration and 1.5 cm. in diameter was excised from the dorsum of the hand of a man of 56, who was a gasworks employee handling tar.

The epithelium.—The tumor is a highly differentiated, epidermoid carcinoma, with broad downgrowths to a uniform depth in the dermis, and

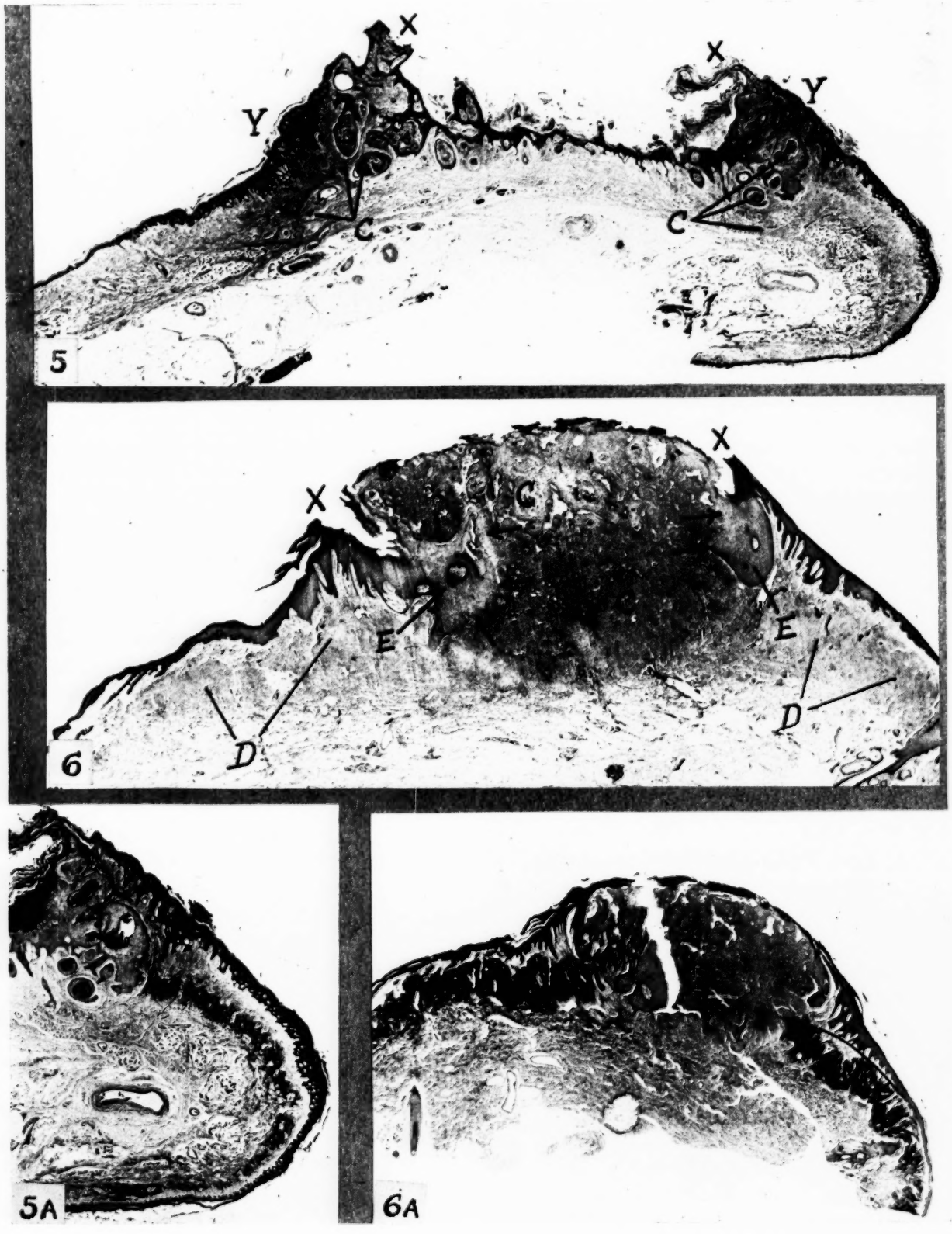

Fig. 5.—Case V. XY, transition zone. CC, deeply penetrating cancerous downgrowths. Mag. × 5.

Fig. 5A.—Same section as Fig. 5, showing darkly stained, thick layer of subepithelial elastic tissue (Verhoeff's stain). Mag. × 6.

Fig. 6.—Case VI. XX, crater lips. EE, marginal epidermis-like downgrowths. CC, more active carcinoma, sharply delimited from E at the arrows. DD, thick layer of altered elastic tissue visible. Mag. × 8.

Fig. 6A.—Elastic tissue shown in Fig. 6 darkly stained by Verhoeff's stain. Mag. × 6.

covered on the surface by a thick layer of keratin. Some of the downgrowths in the central parts of the tumor (*e.g.,* those marked CC in Fig. 2) show some histological evidences of malignancy, namely widespread incomplete keratinization, large irregular spinous cells, and some nuclear irregularities in the marginal cells. But others of the downgrowths (*e.g.,* those marked EE) show perfect epidermal differentiation of spinous, granular, and horny layers. The surrounding epidermis shows gradual hyperplastic thickening as it approaches the tumor, and there is a gentle transition from nonneoplastic to neoplastic epithelium. In the superficial central parts of the growth, also, no sharp distinction is possible between residual nonneoplastic surface epidermis and the cancerous downgrowths from it.

The dermis.—Beneath both the growth and the hyperplastic epidermis there is an abundant infiltration by plasma cells accompanied by fewer lymphocytes. The dermal elastic tissue shows decided increase, with swelling and partial fusion of its fibers, to form a well-marked, pale blue layer in the hematoxylin eosin-stained tissues. This extends with slight diminution in thickness to the edges of the section, at the extreme periphery of which it is unaccompanied by round cell infiltration. The elastic layer has been invaded and destroyed by the cancerous downgrowths.

Case III. (section no. 5734)

A horny "papilloma" 1.5 cm. in diameter was removed from the forearm of a man of 49. A small, scaly nodule had been present for 4 years and had enlarged in the last 3 months.

The epithelium.—The structure of the bulk of the tumor accords with the clinical diagnosis; it is highly differentiated and epidermis-like and consists of large, regular downgrowths between exaggerated dermal papillae. That the tumor is really cancerous, however, is shown by invasive disruption of the dermis by the downgrowths, and especially by the presence of multiple small foci of histologically frank carcinoma at the margins of some of the downgrowths (CC in Fig. 3). These foci, while still epidermoid in structure and continuous with the well-differentiated epithelium without sharp demarcation, show groups of anaplastic cells with irregular or multiple hyperchromatic nuclei and many mitotic figures. These foci clearly possess increased invasive powers, for they have extended into the dermis to a deeper level than that of the general depth of the major downgrowths, and in finer strands of epithelium.

The adjacent epidermis as it nears the growth shows gradual increase in thickness, and this hyperplastic epidermis shows no sharp demarcation from the neoplastic epithelium. Surface keratinization is abundant.

The dermis beneath the tumor proper and the hyperplastic epidermis immediately contiguous with it shows an abundant infiltration of lymphocytes, plasma cells, and eosinophile cells. Except where it is disrupted by the downgrowths of the tumor, the dermis shows a well marked layer of excessive elastic tissue with swollen fibers. This changed elastic tissue is most prominent and thickest close to the growth, but it extends right to the cut edges of the section, and on one side extends beyond the limits of leukocytic infiltration.

Case IV. (section no. 1852)

A wart-like growth of 8 months' duration was excised from the dorsal aspect of the wrist of a man of 46. It was a non-ulcerated projecting mass nearly hemispherical in shape and 1.5 cm. in diameter, with much of its surface presenting a mass of rough keratin. This broke away when the tumor was being sectioned, leaving the symmetrical crater seen in Fig. 4.

The epithelium.—The tumor is a well differentiated epidermoid carcinoma composed of short, stout downgrowths invading the dermis to an evenly uniform depth. Most of these downgrowths in the central part of the tumor are histologically cancerous, although well differentiated, consisting mainly of large, coarsely spinous cells and showing widespread but incomplete keratinization. Mitotic figures are present in moderate numbers, especially in cells along the margins of the downgrowths; some of them show abnormal, *e.g.,* triad, forms. Others of the downgrowths show complete differentiation, with the formation of normal looking spinous cells, a stratum granulosum, and sharply delimited central keratin pearls. Where these normal looking downgrowths are in continuity with clearly cancerous ones, the epithelium shows a gentle transition. The epidermis peripheral to the crater margins, XX, shows gradual hyperplastic thickening as it approaches the growth, but there is no clearly cancerous epithelium external to the crater. On the other hand, it is not possible to assert that all the epithelium within the crater is cancerous. Indeed, some of the more superficial epithelium in the crater floor, as at EE, has all the appearance of residual noncancerous epidermis, in continuity with, and without clear demarcation from, its cancerous downgrowths. Similarly in the neighborhood of the lips of the crater, XX, there is a gentle transition from noncancerous to cancerous epithelium. Observe, also, how just peripheral to the crater edge the epidermis in the zone XY is thinner than the more peripheral hyperplastic epidermis. Underlying this thinned zone of epidermis is the peripheral part of the growth where it invades the dermis.

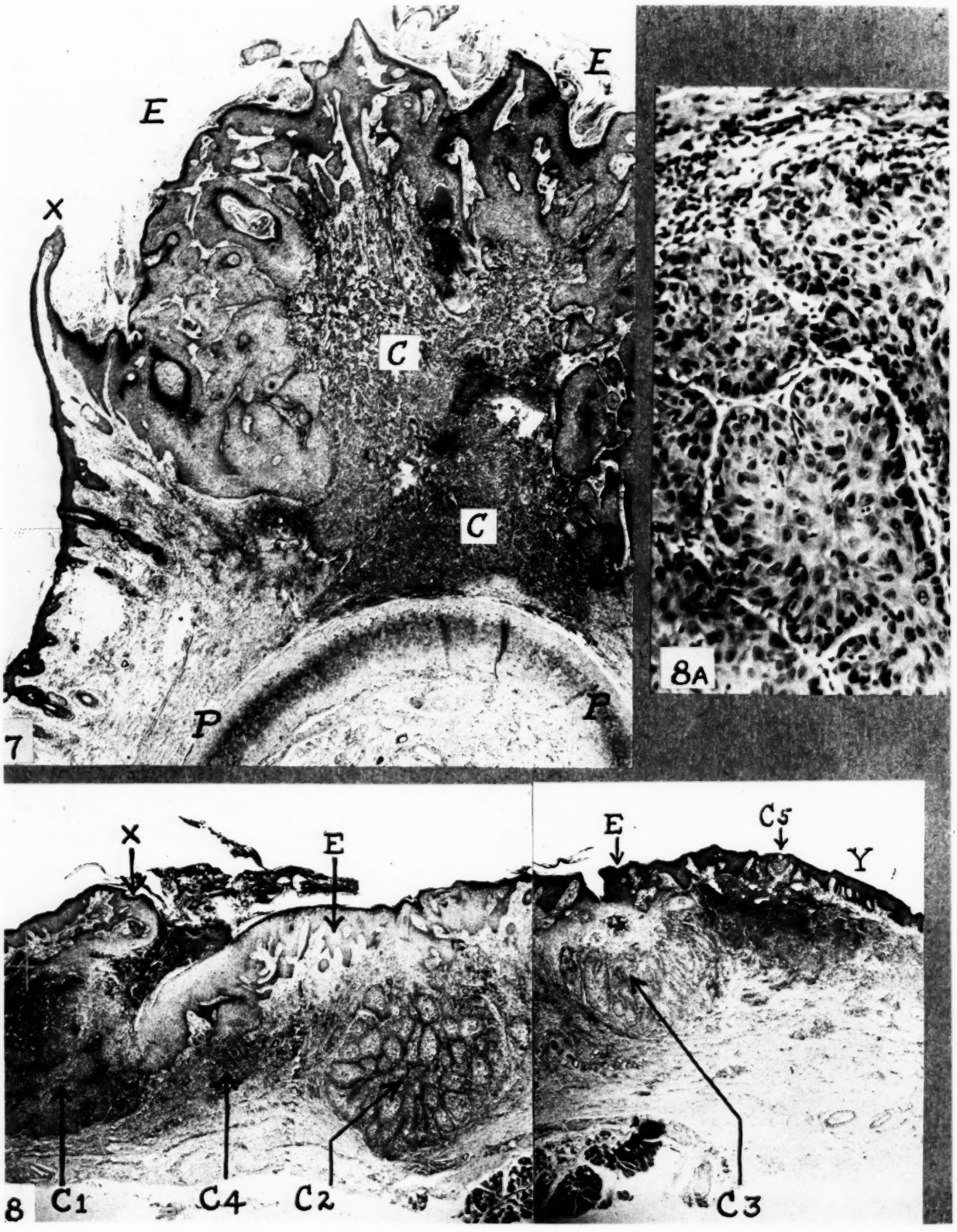

FIG. 7.—Case VII. Vertical section of slightly more than one-half of the growth. X, invagination lip. EE, surface zone of epidermis-like growth. CC, more active carcinoma. PP, cartilage. Mag. × 16.

FIG. 8.—Case VIII. X, invagination lip. Y, region of neoplastic transition without invagination. EE, surface epithelium potentially or actually cancerous. C1, 2, 3, 4 and 5, foci of active carcinoma. Mag. × 12.

FIG. 8A.—Structure of actively cancerous foci shown in Fig. 8. Mag. × 160.

The dermis around the clumps of growth and beneath the thickened marginal epidermis is infiltrated by plentiful plasma cells and a few lymphocytes. There is a slight increase in the number and thickness of the dermal elastic fibers around the tumor margins, unaccompanied in the more peripheral parts by round cell infiltration.

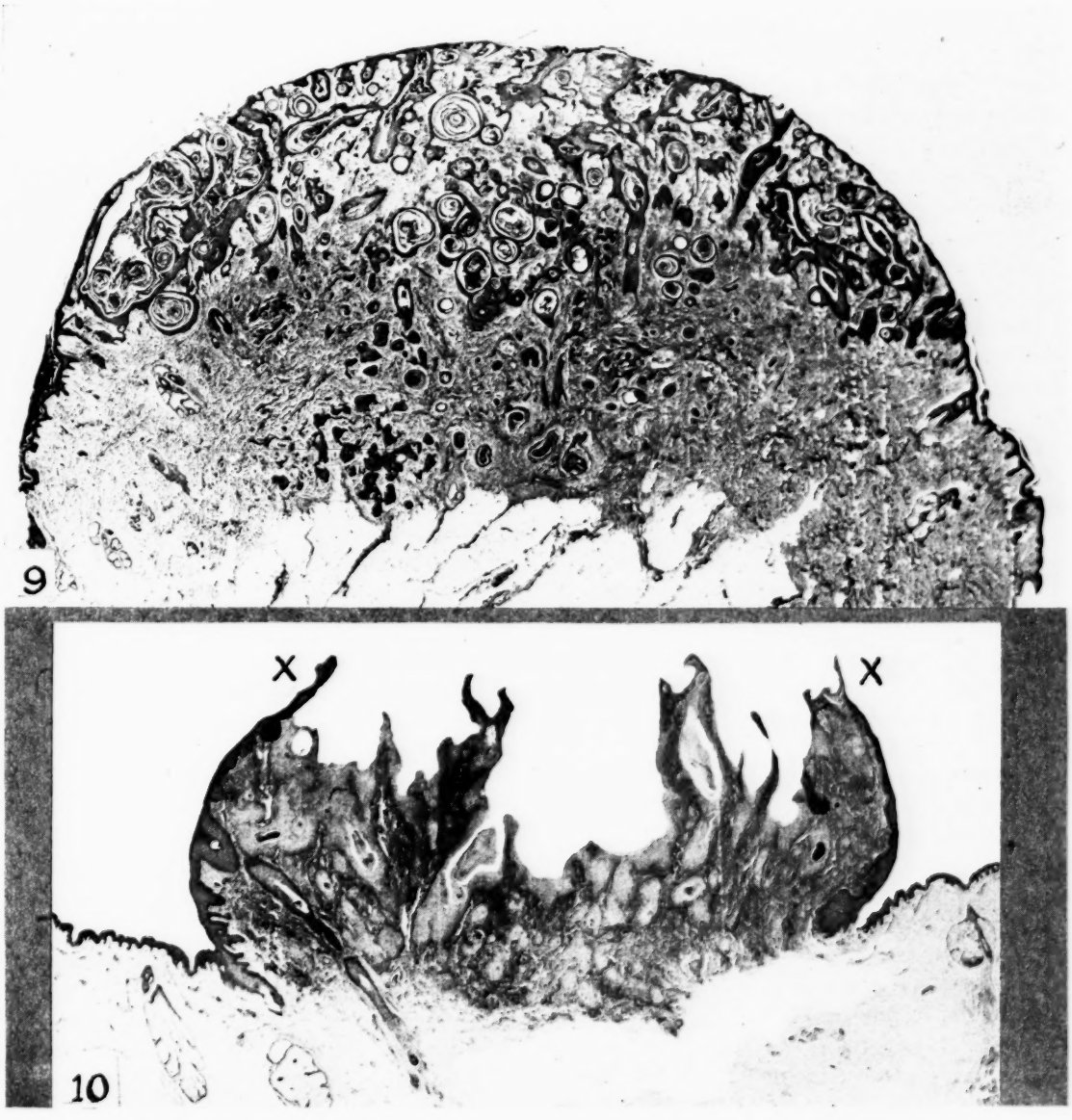

Fig. 9.—Case IX. Vertical section. Mag. × 8.
Fig. 10.—Case X. XX, invagination lips of the protruding growth. Mag. × 10.

Case V. (section no. 3569)

A woman of 75 had noticed an enlarging growth on the dorsum of the wrist for 3 months. She also had multiple hyperkeratoses on the dorsa of the hands and on the face. The projecting hemispherical tumor, which measured 2 cm. in diameter and had a horny summit, was excised along with a wide margin of skin. The horny material was detached during preparation, leaving a crater as shown in Fig. 5.

The epithelium.—As the growth is approached from the periphery of the section, the epidermis shows gradual hyperplastic thickening to about the region of Y, between which and the crater-margin, X, the epithelium becomes thinner again but very irregular. In zone XY it is impossible to decide whether the epithelium is hyperplastic or neoplastic; it is this zone that immediately overlies the most marginal of the carcinomatous clumps invading the dermis. The epithelium in the floor of the crater is complete, thin, perfectly differentiated, and indistinguishable from normal or hyperplastic epidermis. Yet that it is cancerous is shown by its having penetrated into the

dermis, interrupting the dermal elastica (Fig. 5A), and by its having given off the obviously cancerous downgrowths CC. These downgrowths themselves are highly differentiated, showing all the characters of epidermis; namely, normal looking spinous cells, a well-marked stratum granulosum, and sharply limited stratum corneum in the form of concentrically laminated keratin pearls. Extending from their deepest parts, however, lie small clumps of deeply penetrating carcinoma cells with imperfect differentiation and many mitoses.

The dermis.—Abundant lymphocytes along with some plasma cells lie beneath the cancerous area and the adjacent zone of hyperplastic epidermis. The dermal elastic tissue is notably increased, forming a prominent layer up to 1.5 mm. thick extending with gradual diminution of thickness from the neighborhood of Y to the edge of the section (Fig. 5A). Its fibers are enlarged and distinct in most situations, but there are patches of degeneration and hyaline fusion. In the peripheral parts of the section the altered elastica is unaccompanied by round cell infiltration.

Case VI. (section no. 2126)

A hemispherical growth 1 cm. in diameter, of unrecorded duration, was excised from the neck of a man aged 70.

The epithelium.—As the surrounding epidermis approaches the growth, it shows steady hyperplastic thickening. At about XX in Fig. 6 this thickened epidermis passes insensibly, and without change of cytological characters, into the bulky downgrowths EE that form the marginal parts of the growth. That these downgrowths are cancerous in spite of their complete epidermal differentiation, is clear from their penetration into the dermis with interruption of the elastica (Fig. 6A). The bulk of the central part of the growth, CC, consists of moderately active, histologically frank carcinoma, composed of closely packed anastomosing strands and masses of imperfectly formed spinous cells with patchy, incomplete keratinization and a moderate number of mitoses. Between the bulky marginal downgrowths, EE, and this frankly carcinomatous tissue there is an abrupt transition, shown by the arrows in Fig. 6.

The dermis.—Plentiful lymphocytes and plasma cells underlie the growth and the hyperplastic epidermis marginal to it. The dermal elastic tissue is greatly increased in amount and shows advanced degeneration, with swelling and fusion of fibers to form an almost homogeneous layer up to 2 mm. thick. In hematoxylin-eosin-stained sections this forms a prominent blue zone, visible at DD in Fig. 6, but more strikingly shown by Verhoeff's stain in Fig. 6A. This altered elastic layer is interrupted by the downgrowing tumor, from which it extends prominently with slight diminution in thickness to both edges of the section. In the more peripheral parts it is unaccompanied by leukocytic infiltration.

Case VII. (section no. 4582)

A projecting, rough-surfaced, hemispherical growth 8 mm. in diameter, of unspecified duration, on the outer edge of the pinna of the ear of a man of 57 was diagnosed as a "papilloma" and excised.

The epithelium.—A vertical section through the middle of the growth (Fig. 7) shows the following structure. At X the epidermis, which shows little or no hyperplastic thickening, undergoes a sharp invagination and becomes continuous with a layer of greatly thickened convoluted epidermis, EE, that clothes and forms the surface zone of the growth. This layer exhibits perfect differentiation of all the characters of epidermis, and shows no cytological signs of its neoplastic quality. That it is cancerous, however, is shown by its great thickening, its irregular downgrowths into the dermal tissues, and the continuity of these downgrowths with a mass of frankly carcinomatous tissue, CC, that constitutes the central part of the growth and extends down to the cartilage of the pinna, PP. This carcinomatous tissue consists of closely aggregated, narrow, epithelial columns devoid of epidermal characters except for occasional small foci of keratin and a few poorly formed spinous cells. The cells show considerable variation in the size of their nuclei, and mitoses are fairly numerous. The zone of junction of this tissue with the overlying epidermis-like zone EE shows rapid, but not abrupt, transition from the one to the other; the columns of the frankly cancerous tissue are but tendril-like continuations of the deeper parts of the downgrowths of EE. This is clearly shown in the figure.

The dermis.—Beneath the infiltrating edge of the growth and the epidermis at its margins there is a plentiful collection of lymphocytes accompanied by a few eosinophile leukocytes. The dermal connective tissues show some fibroblastic thickening and the formation of many small blood vessels. There is no evidence of any great change in the dermal elastica.

Case VIII. (section no. 5650)

A slightly raised, circular growth 1.5 cm. in diameter, with a flat, encrusted surface was excised from the neck of a man of 70.

The epithelium.—A vertical section through the center of the growth shows most of its surface to be clothed by a perfectly differentiated but thickened and very irregular epidermis-like layer, EE, which is continuous peripherally with the slightly thickened hyperplastic epidermis around. The transition from the one

to the other, which is gradual and without any change of cytology, takes place in the neighborhood of the points X and Y. At X the transition takes place fairly rapidly and is accompanied by a sharp invagination of the epithelium; at Y the transition is much more gradual and there is no invagination. It is impossible to decide whether the epithelium EE is extravagantly hyperplastic or already neoplastic; but springing from its deep surface there are multiple frankly cancerous downgrowths. There are at least 3 quite separate downgrowths, C1, C2, and C3; while at C4 there is another small carcinomatous patch probably, but not certainly, separate from C1; and at C5 there is a minute probably carcinomatous focus in the epidermis. The carcinoma C1 penetrates the dermis almost to reach the platysma. The characters of the frankly malignant tissue are similar in all the foci, and are shown in Fig. 8A. It consists of epidermoid carcinoma of active type with abundant mitoses, many large, coarsely spinous cells, and patchy, imperfect keratinization. Although this carcinomatous tissue is quite distinct in structure from the well-differentiated surface epithelium, the region of junction of each cancerous area with this epithelium shows a gentle, though rapid, transition from one to the other.

The dermis.—Lymphocytes and plasma cells are plentiful around the carcinomatous areas, but are few elsewhere and are not present in the dermis away from the growth. The dermal elastica shows decided increase and degeneration, appearing in hematoxylin-eosin-stained sections as a prominent, lilac-blue layer up to 1.5 mm. thick. This consists partly of greatly swollen but still separate elastic fibers, and partly of structureless hyaline material formed by fusion of the fibers. The layer of altered elastica is interrupted by the cancerous downgrowths; peripheral to these it is continuous and prominent, with some diminution in thickness, right to the edge of the section.

Case IX. (section no. 4799)

A growth of several months' duration was excised from the neck of a woman of unrecorded age. It was a nonulcerated, projecting, smoothly hemispherical mass 2 cm. in diameter.

The epithelium.—The marginal epidermis, which shows slight thickening as it approaches the tumor, passes insensibly into the thin but complete layer of epithelium that covers the tumor surface. The rest of the tumor consists of irregular, ramifying downgrowths from this layer. These downgrowths, though clearly cancerous, show almost perfect differentiation of all the features of normal epidermis, including perfectly formed spinous cells, a stratum granulosum, and abundant keratinization forming laminated, sharply defined, epithelial pearls. Mitotic figures are few. The thin surface layer of epithelium also shows complete epidermal characters, and it is impossible to decide where marginal noncancerous epidermis ends and cancerous epidermis begins, or even to exclude the possibility that the surface layer may consist only of stretched residual noncancerous epidermis.

The dermis shows general fibrous thickening forming the stroma of the growth, and this is infiltrated by many plasma cells and lymphocytes. Associated with some of the carcinomatous clumps in which degenerating keratin and some calcification are present, there are a few foreign body giant cells and some polymorphonuclear leukocytes. The elastic tissue of the dermis marginal to the tumor shows only slight increase.

Case X. (section no. 7171)

A slightly pedunculated, nearly hemispherical growth, 1 cm. in diameter, of unrecorded duration, was excised from the skin of the dorsal aspect of the neck of a woman aged 35. The summit of the growth was clothed by a rough mass of keratin, which was detached during preparation.

The epithelium.—The tumor is an epidermoid carcinoma of fairly well-differentiated type. Although its downgrowths penetrate into the dermis of the pedicle only slightly below the surface level of the surrounding skin, histologically they are clearly cancerous, being very irregular, tendril-like and anastomosing in places, with patchily imperfect differentiation. In the floor of the crater left in the summit of the growth by detachment of the keratin the epithelium, though irregularly festooned and papillated, is well differentiated and epidermis-like. The epithelium clothing the sides of the growth, from its base to the edges of the crater, XX, is smooth-surfaced, devoid of excessive keratin, and histologically identical with the adjacent normal epidermis except that it shows moderate hyperplastic thickening. The surrounding epidermis appears quite normal.

The dermis.—The exaggerated papillae and connective tissue strands between the tumor downgrowths are heavily infiltrated by lymphocytes together with a few plasma cells and polynuclear cells. Many of the epithelial cords are invaded and partly disorganized by collections of these leukocytes. Slight perivascular collections of leukocytes are present in the dermis peripheral to the growth. No changes are detectable in the dermal elastica either beneath the growth or in the surrounding skin.

DISCUSSION

A. Review of the Specimens

I contend that in none of the specimens described can the structure be plausibly explained in terms of

the hypothesis of simple unifocal, unitemporal origin and purely intrinsic proliferative growth. Let us review the structure of our specimens from this aspect, comparing and contrasting the figures.

Tumors I, II, and III, all from the forearm or hand, closely resemble one another in structure. All 3 consist of highly differentiated, slowly growing epidermis-like tissue of relatively low invasive power. This tissue, together with its overlying keratin, forms in each case a complete nonulcerated hemispherical mass in continuity with the surrounding epidermis, of which it constitutes a symmetrical thickening, with extravagant papillation and keratinization, over a circular field between 1 and 2 cm. in diameter. In each case the surrounding epidermis shows gradually increasing hyperplastic thickening as it approaches the growth, and this hyperplastic epidermis passes gradually into the cancerous epithelium, making it impossible to decide just where the one ends and the other begins.

This structure is incompatible with the view that the tumors arose each from a minute central focus and grew solely by invasive replacement of surrounding epidermis. Even if we supposed the neoplastic cells sprouting out from such a hypothetical focus to spread preferentially within, and to effect cell by cell replacement of, the invaded epidermis (a process for which none of the specimens studied affords any evidence), this would still not suffice to explain the gradual transition from hyperplastic to neoplastic tissue and the absence of any clear, or even approximate, region of demarcation between the two. Each of these growths shows plain evidence of a progressive hyperplastic-neoplastic change, still taking place, in a centrifugal direction over a field of epidermis greater in extent than the present size of the growth. In Borst's words, "the tumor-formative field has not yet been totally incorporated in the growth". The actual size of the potential tumor-formative field in each of these specimens is an area of epidermis clearly at least 1.5 cm. in diameter, and probably much greater than this, since there is a considerable zone of epidermal hyperplasia around each growth, and there is no reason to suppose that we have chanced to examine the tumors just at the time when the neoplastic potentiality of this zone is nearing exhaustion.

Tumors IV and V, while showing a general similarity to the previous specimens, present also certain interesting differences. Similar are the high degree of epidermis-like differentiation of the growths, the presence of a peripheral zone of hyperplastic epidermis steadily increasing in thickness as it approaches the growth, and the absence of any clear demarcation between hyperplastic and neoplastic tissue in the zone YX. Different from the previous specimens are the diminished thickness of the epithelium in the hyperplastic-neoplastic zone YX, the relatively small thickness of the cancerous epidermis in the floor of the crater left after removal of the large mass of superjacent keratin, and the sharp invagination of the epithelium at the crater edge, X. It is as if the area of cancerous epidermis, while undergoing great hyperkeratosis but without much proliferative increase in bulk, and while still retaining its marginal continuity with the surrounding hyperplastic epidermis at the invaginating edge, X, had sunk as a whole into the subjacent dermis. In each specimen the most peripheral cancerous downgrowths invading the dermis underlie the thinned but irregular zone of surface epithelium, YX, which is itself in gentle continuity with the more peripheral zone of thick, hyperplastic epidermis.

These very distinct structural characters cannot be dismissed as merely fortuitous, and they are inexplicable on the hypothesis of origin from a tiny central focus and growth by proliferative invasion of surrounding tissue. On the basis of progressive genesis still taking place in a field of tissue, however, these characters at once become intelligible. From the structure of the central parts of these two tumors it is clear that their habit of growth is to produce a relatively thin depth of invading epithelium, surmounted by a large mass of keratin. The thinned, irregular epidermal zone YX is a zone of transition from much thickened but only hyperplastic epidermis on the one hand to clearly cancerous invasive epidermis on the other. As the epithelium of this zone progressively acquires frankly neoplastic properties it invaginates itself at the crater edge, X, and so joins the already invasive neoplastic epithelium in the sides and floor of the crater. It is from these sides and this floor that cancerous downgrowths sprout. Thus the conception of progressive cancerization extending concentrically over a widening area of epidermis affords a clear explanation of the structure of these growths. The diameter of the field that has already become cancerous is 1.5 cm. in Case IV and 2 cm. in Case V; and, especially in Case V, the changes in the surrounding epidermis strongly suggest that the potentially cancerous field is much greater still.

Tumors VI and VII. In the interpretation of these two specimens, a minor feature exhibited by III and V deserves further notice. This is the presence in the deepest parts of the growths of small foci of cancerous epithelium of poorer differentiation and greater mitotic activity than the remainder of the tumors. These small anaplastic foci clearly denote an early stage of augmented growth rate and degree of malignancy in parts of these tumors. Such enhanced malignancy with respect to the earlier established, less active parts is seen in a more advanced stage in VI and VII.

In tumor VI, as in the previous specimens, there

is a marginal zone of hyperplastic epidermis that passes insensibly into the epidermis-like downgrowths of the peripheral parts of the tumor. Like specimens IV and V, also, the cancerous epithelium shows invasive invagination, forming sharp crater lips, XX. The bulk of the central parts of the tumor, however, consists of much more active, poorly differentiated carcinoma, and there is an abrupt junction between this and the epidermis-like marginal parts of the tumor. The structure of the tumor thus indicates its development in two stages, namely: (a) a stage of transformation, still in progress, from hyperplastic epidermis to well-differentiated epidermoid carcinoma with invagination and downgrowth of the latter, EE; and (b) a supervening accession of growth rate and malignancy, with corresponding dedifferentiation in the central part of the growth and invasive replacement of the well-differentiated growth, EE, by the more anaplastic component, CC. Incidentally, this specimen affords a good example of the abrupt junction created when a relatively quiescent epidermal tissue suffers proliferative invasion and replacement by active carcinoma. It is this kind of junction that we should regularly see were the strict unicentric view correct, but which, as this study shows, is not observed in early epidermal carcinomas.

A similar two-stage sequence accounts for the structure of growth VII, which, however, shows some further noteworthy features. Here the initial stage of conversion of hyperplastic into neoplastic epidermis appears to be complete, for there is no zone of hyperplastic epidermal thickening peripheral to the invagination lip, X. The whole of the potentially cancerous area has been converted into tumor, the first stage of which is represented by the greatly thickened, irregularly folded layer of epidermis-like growth, EE. The deeper parts of the tumor, CC, which are of much more active and poorly differentiated type, have clearly arisen by a supervening accession of malignancy in the downgrowths of EE; and it seems clear that this has occurred not at a single spot but in a widespread manner.

On the hypothesis of simple unicentric origin and purely intrinsic proliferative growth, neither the general structure nor the dual character of the neoplastic tissue in tumors VI an VII is intelligible. The conception of cancerization of a field of epidermis, with supervening augmented growth rate in the same field, however, readily accords with the structure observed.

Tumor VIII is of great interest in that it shows multiple, separate foci of histologically frank carcinoma springing from the deep surface of a considerable area of hyperplastic (or possibly neoplastic) epidermis. These little separate carcinomas all consist of similar, rather active, tissue; and all show a similar relation to the surface epithelium, with a rapid but not abrupt transition from one to the other. The nature of the surface epithelium itself, whether only hyperplastic or already neoplastic, is not certain for the same reason that in previous specimens it has been impossible to say precisely where hyperplasia ends and neoplasia begins, save by the invasive powers displayed by the epithelium. However, that the surface epithelium in the present specimen is potentially, if not actually, cancerous is shown by its having given origin to multiple clearly carcinomatous downgrowths, while the presence of an invaginating lip at X points strongly to genuinely carcinomatous properties. In the light of the two previous specimens we may strongly suspect that here, too, we are witnessing a two-stage transformation comprising: (a) a hyperplastic-neoplastic change in the entire field of surface epithelium, accompanied at X by invasive downgrowth; and (b) the supervention of enhanced growth-rate, with invasive powers at multiple spots in the deep parts of the already unstable epidermis. It can scarcely be doubted that, had this lesion not been excised, more and more of this unstable epidermal field would have passed into frank carcinoma.

Tumor IX shows characters rather different from those of the previous specimens. The marginal epidermis shows only a little hyperplastic thickening, but as it is traced onto the surface of the growth it is impossible to decide even approximately where noncancerous epithelium ends and cancerous begins. The ramifying cancerous downgrowths themselves show perfect histological differentiation, and are connected with the surface epithelium at many points and in a uniform manner over the whole extent of the growth. It is difficult to picture how this tumor could have developed by purely proliferative growth from a single minute focus, but easy to understand how it could have arisen progressively from a field of epidermis coextensive with it, *i. e.,* a circular area 2 cm. in diameter.

Tumor X is unlike any of the other specimens in that, while its tissue histologically is clearly cancerous, it has failed to effect invasion of the dermis; its growth has been almost wholly outwards and it has attained a pedunculated form. Hyperplastic epidermis clothes the sides of the projecting growth, but the surrounding epidermis shows no alteration. In other respects the structure resembles that of IV and V, with a similar continuity of hyperplastic epidermis with cancerous epithelium at sharp crater edges XX. The growth is to be interpreted as arising from a field of epidermis coextensive with it; much of this field has already become cancerous, but the residual hyperplastic epidermis on the sides of the tumor has yet to become so. In spite of the invasive invagination dis-

played by the cancerous epithelium, it has failed to penetrate the dermis but has suffered instead a kind of partial extrusion on the surface as it grew. We shall return to this feature presently in considering the dermal changes.

B. Changes in the Epidermis

A striking feature of many of these early growths is the retention of almost perfect epidermis-like structure by the cancerous epithelium. This may show distinctly the various strata of the epidermis, as well as cell details such as spines, keratohyalin granules, and nuclear characters identical with those of normal cells. Mitotic figures are often little or no more numerous than in the adjacent normal or hyperplastic epidermis. Indeed, the histology of the epithelium alone, without reference to its position, often gives no indication of its neoplastic qualities. This nearly perfect epidermal structure is retained because the tumor actually consists of a field of cancerized epidermis. In this field cellular structure, arrangement, and rate of multiplication may have undergone but little change; most of the tissue of the growth represents the preexisting tissue transformed, and not a proliferated colony of descendants of a single cancerous mother cell.

Of course it is not denied that an established tumor grows in bulk by cell proliferation in excess of that of the normal epidermis, or that proliferating tumor tissue also may attain a high degree of epidermoid differentiation. What is to be insisted on, however, as clearly revealed by the specimens described, is that a skin cancer in its early formative stage arises more by a gradual transformation of preexisting epidermis than by cellular multiplication, and that only after the formative field has all suffered neoplastic change does the tumor grow solely by multiplication. The two processes, neoplastic transformation and increased cellular multiplication, overlap, the former predominating during the early genesis of the tumor, the latter often being initially negligible but gradually taking an increasing and finally exclusive part in the growth of the tumor. As specimens III, V, VI, VII, and VIII show, an established growth may exhibit acceleration of its rate of proliferation, with corresponding structural anaplasia and, no doubt, enhanced malignancy.

It is relevant to refer here to the distinction between "benign" and "malignant" neoplasia. Such tumors as I, II, and III are superficial, clinically innocuous lesions with no risk of metastasis, and are looked upon by the surgeon as benign. Yet to the histopathologist they are cancerous, because the epithelium has penetrated into and disrupted the dermis. Are they "papillomas with early malignant changes," or are they lowly malignant carcinomas *ab initio*? The distinction is merely verbal; "innocent" and "malignant" are only relative terms, clinically useful in prognosis but not denoting sharply separable classes of tumors. An epidermal "papilloma" differs from a carcinoma only in that the invasive power of the neoplastic epithelium is slight or for the time being in abeyance; the noninvasive growth of today may display its invasiveness tomorrow, and this display does not mean that the cells of the growth have suddenly acquired new properties. It is futile, then, to try to decide how much of the neoplastic tissue in growths like those described is "papillomatous" and how much is "carcinomatous." The epithelium shows a steady progressive change, commencing with preneoplastic hyperplasia and culminating in invasive carcinoma.

C. Changes in the Dermis

Increase and degeneration of the dermal elastic tissue were prominent in most of my specimens. In assessing the possible significance of these, it was first necessary to ascertain their frequency and degree in noncancerous skin. Various surgically removed skin lesions were examined, and also pieces of skin removed postmortem from the neck, forearm, hand, and leg of 20 middle-aged or old subjects. The skin of the dorsum of the hand and forearm in the elderly often showed pronounced changes in the elastic tissue, resembling those seen in association with carcinomas; the skin of the neck showed such changes less frequently; the skin of the leg seldom showed prominent changes.

Although nearly all my tumors were from the hand, forearm, or neck, regions where senile changes in the elastic tissue are commonly present, there are two strong reasons for believing the dermal changes in the tumor specimens to be at least in part related to the tumors and not wholly coincidental: (a) In several cases, I, V, VI, and VIII, the thickness of the altered elastica near the growth was greater than in any of the noncancerous control specimens examined; and (b) in most cases its thickness was greatest close to the growth and diminished towards the edges of the sections.

There are two possible ways in which these dermal changes might be related to the tumors; either they might be secondary, part of the stromal reaction to their presence, or they might have preceded the formation of the tumors, being part of the precancerous state in the fields in which the tumors later developed. While the first possibility cannot be excluded, I lean to the second for the following reasons: (a) Changes in the dermal elastica, clearly related to the growth because showing diminution in a centrifugal direction around it, are often present at considerable distances

from it, 1 cm. or more in several cases, and often beyond the zone of leukocytic reaction to the tumor. (b) There are no comparable changes in the perivascular and interstitial elastic tissue of the deep dermal and subcutaneous tissues beneath the invading tumors, contrary to what might have been expected if the dermal changes were only a stromal reaction to the tumors. The tumor downgrowths make complete breaches in the layer of altered elastica, as if the latter had already been present prior to invasive disruption by the former. (c) Orr (17) has shown that the precancerous changes following the experimental application of carcinogenic hydrocarbons include prominent, and apparently specific, alterations in the dermal connective tissues, including the elastic, and that "when tumours appear, they are frequently related to fibrous scars in the subcutis, to gaps in the elastic tissue of the dermis, or to both." Allowing for the structural differences between mouse and human skin, there is a close parallelism between Orr's experimental results and my own observations, especially as regards the elastic tissue changes. The experimental findings strongly support the view, reached from the purely structural evidence given above, that the changes in a potentially cancerous field of skin include alterations of the dermis and that these play a part in the inception of tumors.

It may well be that carcinogenesis involves not only augmented epithelial growth but also, as Ribbert long ago supposed, diminished connective tissue restraints. Perhaps the peculiar structure of my specimen X was determined by an unusual retention of the restraining capacity of the dermis, so that invasion was deferred and the cancerous epithelium could only grow outwards as it multiplied. Certainly this specimen was also unusual in the absence of any visible changes in the dermal elastic tissue.

D. Conclusion

I believe that the evidence advanced justifies the view that squamous cell carcinomas of the human skin are comparable with those produced experimentally, and are the products of the following sequence of events:

(a) A skin field more or less extensive has been subjected to a succession of carcinogenic stimuli (still often unspecifiable in human beings), which have induced slow progressive changes in both the epidermis and dermis of that field. With the passage of time the epidermal changes become structurally apparent as precancerous hyperplasia, which may persist innocuously as such for long or brief periods. The dermal changes include gradual increase, followed by degeneration, of elastic tissue just below the epidermis. In this precancerous field there is often a visible gradient of both epidermal and dermal changes, usually from a single central focus to the periphery, but sometimes with more than one focus of high cancer potential.

(b) At the central focus (or at several high potential foci) of the field, hyperplasia passes into irreversible neoplasia, with or without immediate invasion of the dermis by the epithelium. Invasion probably commences at points of maximum damage of the dermal elastic tissue.

(c) As cancerous proliferation and invasion progress at the central part of the field, cancerous change of the surrounding unstable epidermis takes place in a steadily enlarging area around the centre. It is at this stage that early carcinomas of the human skin, like those described, become available for study.

(d) After the entire field of the predisposed epithelium has become cancerous the tumor enlarges solely by proliferation of the cancerous cells, and structural evidence of its mode of origin is soon lost.

One final point requires clarification. Some pathologists (*e. g.,* Welsh, 18), while properly recognizing that tumors often arise by spreading cancerization of a more or less extensive field of tissue, have assumed this to be brought about by "the passage of a malignant influence from cancer cells to adjacent noncancerous epithelial cells, whereby the latter are induced to become cancerous *in situ*." However, there is no need to create a stumbling block by supposing any such "malignant influence." In human as in experimental carcinogenesis the effective stimuli are applied, not to one cell or one small group of cells, but to a more or less extensive area of epithelial tissue. All the epithelium in that area is acted upon similarly, though of course usually not equally. Neoplasia will commence where the stimuli have been maximal, but the neoplastic response will later be manifested by neighboring tissue that was subjected to the same original stimuli. The timing and distribution of this progressive response will depend on the distribution and intensity gradients of the causative stimuli.

SUMMARY

1. The structure of a series of early, localized squamous cell carcinomas of human skin is described, including the dermal as well as the epidermal changes.

2. The structure of these growths is incompatible with a strict unicentric view regarding their origin, but shows instead that each has arisen by spreading cancerization of a field of epidermis. Such cancerization usually commences from a single central focus, but several initial foci may be present.

3. The precancerous state of an area of skin includes significant dermal changes, especially in the subepithelial elastic tissue, and invasion of the dermis

by the cancerous epithelium probably commences at points of greatest damage of the dermal elastica.

4. Progressive neoplasia in a field of tissue does not imply the passage of any carcinogenic stimulus from cell to cell, but is merely the progressive response of an area of epithelium to the same original stimuli, a response graded according to the gradients of the effective stimulation.

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The Distribution of Iron and Copper in Malignant Neoplastic Disease

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Iron and copper in varying concentrations are required for certain vital processes in the human organism. For some time the importance of iron has been appreciated as a constituent of hemoglobin, which transports oxygen and carbon dioxide to and from the tissues. More recently iron in smaller quantities has been identified as part of the catalase and cytochrome molecules and Warburg's respiratory enzyme. In 1931 Lintzel (19) wrote a lengthy review on the assimilation, utilization, and excretion of iron by the human body. Lehmann (18), in a review on the occurrence of copper in plants and animals, credits Devergie with the first detection of copper in human tissues, in 1838. In hemochromatosis Mallory (20) found greater amounts of copper than normal in the liver. Until Hart and his associates (13) pointed out that copper is necessary for hemoglobin formation, no biochemical function had been ascribed to it, and it had been considered merely a contaminating substance.

The most recent review on the occurrence and biological functions of copper has been written by Elvehjem (9).

Chemical analyses of human organs for iron and copper have seldom been made on the same specimen. The liver has repeatedly been analyzed for one or the other but rarely have iron and copper been determined on the same liver. Some workers have employed material from one or two autopsies to determine iron and copper in the different organs, but a large number of autopsies have not been used to study the distribution of iron and copper statistically in the human body. Accordingly we have investigated the distribution of these two metals in autopsy material from patients with malignant neoplastic disease. The results have been treated statistically. A comparison has been made of the iron and copper in tumors and in other tissues of the body, and the results have been studied to determine if different pathological conditions are correlated with variations in the iron and copper content. Since cancer patients show a tendency to become anemic, we have considered the results of the iron and copper analyses to determine if the anemia comes from a lack of either or both of these elements.

EXPERIMENTAL

Preparation of material.—Tissues for analysis were obtained from autopsies at the State Institute for the Study of Malignant Diseases without regard to the classification of the disease,[1] but not all the tissues were available from each case. As soon as the tissues were obtained all extraneous fat and connective tissue were removed from the organs, and the tumor was dissected from the surrounding tissues as completely as visual inspection would permit. Since preliminary analyses indicated that neoplasms are low in both iron and copper, all the available tumor tissue was employed, so that a sample could be obtained that would furnish amounts of iron and copper large enough for each analysis. As a source of tumor material the primary lesion was always preferred, but in some instances metastatic growths were used. All tissues were cut into slices to permit the complete drainage of blood, minced, weighed, and spread in thin layers on glazed plates, which were then placed in an electric oven maintained at 105° C. After 18 hours the partially dried material was stirred to expose new surfaces. When the tissue had been in the oven for 24 hours it was broken into small pieces in a mortar. After having been dried in the electric oven for an additional 24 hours to attain constant weight, the material was removed and weighed.[2] The moisture content was determined by the loss in weight after the 48 hour drying period. The tissue was then ground in a mortar to a fine, homogeneous powder, but because of their large fat content some livers that had undergone fatty degeneration were difficult to grind so thoroughly. The dried material was stored in tightly corked bottles until the analysis could be done. Just before a sample was removed for analysis the whole mixture was stirred to insure uniformity.

Ashing.—One of the chief obstacles in determining minute amounts of iron and copper in biological

[1] One specimen was obtained from the operating room.

[2] The gallstones were not dried before analysis.

materials has been the destruction of the large quantities of organic matter. When dry ashing has been used the tendency has been to overheat the ash and lose some of the metal by volatilization. Wet ashing methods have the disadvantage that they give values too high because of contamination of the added reagents required for the ignition. We have preferred to use the dry ashing technic with precautions to prevent loss of iron and copper. When sufficient material was available separate samples were ignited for iron and copper analyses. It was desirable to ash samples large enough to yield 0.25 to 0.5 mgm. of iron, and for copper enough to yield 0.1 to 0.2 mgm. The appropriate sample was weighed into a quartz dish of 80 cc. capacity and placed over a Bunsen burner for the initial ignition, which was carried on at a low temperature. The escaping fumes were ignited by this procedure, and a carbonized residue that could be ashed more easily was obtained. After the material had stopped fuming, the quartz dish was placed over a Meker burner and the ashing continued as long as the residue did not fuse. As soon as there was the slightest indication of fusion the quartz dish was removed from the burner. To the cooled carbonized residue 5 cc. of 1,2-hydrochloric acid was added and the residue broken up with a glass stirring rod. Then 10 cc. of distilled water was added, rinsing the stirring rod. The quartz dish was covered with a watch glass and its contents were extracted by setting it in the top of a 400 cc. beaker partly filled with distilled water, which was kept boiling on a hot plate for 30 minutes. The acid extract was then filtered through ashless filter paper (Schleicher and Schüll, 589 Blue Ribbon, 9 cm. diameter). The dish was washed with several portions of hot distilled water, and each portion passed through the filter containing the carbon residue. In all about 75 cc. of hot water was used to wash the dish and filter. The filter paper containing the carbon residue was returned to the quartz dish and, after having been dried, the dish was placed in an electric furnace at dull red heat. This ignition was usually complete within 30 minutes. The contents of the quartz dish were extracted as before, and the filtrates from the two extractions combined and evaporated to a volume of 10 cc. By extracting the carbonized ash just before the material fuses the loss of iron and copper by volatilization is reduced to a minimum.

It was found by analyzing the two extracts separately that 90 per cent of the iron and copper were removed in the first extraction. Prolonged heating causes the ash to fuse, and further heating then leads only to increasing losses of iron and copper. This is especially true of tissues with a high phosphorus and low calcium content.

Colorimetry.—For the iron determination the hydrochloric acid solution of the ash was made up to volume. On an aliquot portion equivalent to about 0.05 mgm. of iron the iron was determined according to Elvehjem's modification (8) of the Kennedy (16) method. The copper was isolated by passing hydrogen sulfide into the hot hydrochloric acid solution. A suspension of the resulting copper sulfide in chloroform was washed with acidified hydrogen sulfide water until it was free from iron. The colorimetric determination of the copper was made with the Biazzo reaction, as adapted by Gebhardt and Sommer (10). In some instances only enough material was available for one sample, and in these cases the copper was isolated as described and iron determinations were made on the wash water from the chloroform suspension of the copper sulfide.

Recovery.—To determine the reliability of the methods, known amounts of ferric chloride and copper sulfate were added to the dried material before ashing. The added iron and copper approximated the amounts encountered in the tissue analysis. Analyses for recovery were made simultaneously with the analyses for the respective tissues. There were 75 recovery analyses made for iron, with an average recovery of 98.5 per cent. In all but 2 cases 90 per cent or more of the added iron was recovered, and the recovery ranged as high as 108 per cent. The average for 94 recoveries of added copper was 95.6 per cent; in 12 instances the recovery was below 90 per cent, and it ranged as high as 108 per cent. The excellent recovery obtained can be attributed to the method of igniting the samples. Tests showed that prolonged ignition (avoided in our procedure) led to poor recovery of added metals, in some cases as low as 60 per cent. Recoveries described in the literature have been made only too often by adding the known amount of metal just before developing the color. In this way no check was made on loss of the metal during the ignition of the sample.

Throughout the procedure water redistilled from an all-glass apparatus was used. All analyses were made in duplicate, and if the variation was greater than 10 per cent the determination was repeated. The moisture content is reported as percentage of water, and the iron and copper as milligrams per 100 grams of dry tissue unless otherwise stated.

DISCUSSION

Table I shows the histological diagnosis of the primary lesion and the age and sex of the subjects from which material was taken for analysis. Whenever the percentage of hemoglobin and the red cell counts were available, those determined just before death were included. About 90 per cent of the cases

in this series were carcinomas, the same distribution that has been found at this institution over a long period of time. There were 16 females and 27 males. The youngest was No. 588, a male 21 years old with a diagnosis of lymphoblastoma; the oldest was No. 615, a male 85 years old with an epithelioma of the neck. There were 4 subjects in the third decade, 2 in the fourth, 7 in the fifth, 11 in the sixth, 13 in the seventh, 5 in the eighth, and 1 in the ninth. Table II gives the means, together with their probable errors, of the analyses of the various organs for iron, copper, and moisture.

TABLE I: SOURCE OF MATERIAL FOR IRON AND COPPER ANALYSES

Autopsy No.	Sex	Age	Diagnosis	Percentage hemoglobin	Erythrocyte count	Days before death
601	M	46	Carcinoma, larynx	*		
570	M	52	Epithelioma, "			
603	M	65	Carcinoma, "	52	2,716,000	42
609	M	66	Epithelioma, "			
653	M	49	Carcinoma, stomach	20	1,048,000	7
569	M	63	" "			
678	M	25	Teratoma, testicle	68	3,616,000	53
602	M	37	" "	45	2,880,000	7
669	M	24	Carcinoma, lung	70	4,122,000	9
675	M	65	" "			
579	M	41	Carcinoma, bladder	90	4,672,000	76
677	M	58	" "			
685	M	54	Epithelioma, tonsil			
608	M	61	" "			
652	M	38	Carcinoma, esophagus			
591	M	45	Embryonal tumor, kidney			
648	M	56	Carcinoma, thyroid			
735	M	56	Epithelioma, bronchus			
668	M	60	Carcinoma, rectum			
680	M	68	" prostate			
688	M	70	Epithelioma, pharynx	75	4,352,000	84
615	M	85	" neck			
588	M	21	Lymphoblastoma	70	3,584,000	29
646	M	27	Hodgkin's sarcoma	42	3,104,000	11
583	M	42	Lymphosarcoma	70	3,872,000	1
649	M	68	Adenoma, prostate			
740	M	73	" "			
617	F	42	Carcinoma, breast			
665	F	59	" "			
590	F	73	" "			
683	F	54	Carcinoma, stomach			
744	F	62	" "	50	3,350,000	46
599	F	51	Epithelioma, hypopharynx			
736	F	57	Carcinoma, rectum			
650	F	57	Epithelioma, vagina			
607	F	58	" vulva	58	3,840,000	30
595	F	60	Carcinoma, uterus			
679	F	67	" pancreas	73	4,160,000	4
613	F	69	Adenocarcinoma, ovary			
662	F	73	Carcinoma, bladder	58	3,678,000	8
691	F	47	Myelogenous leukemia	33	2,058,000	15
672	F	67	Sarcoma, pancreas			
645	F	78	Polycystic kidneys	84	4,288,000	2

* Hemorrhage 3 hours before death.

Iron.—The spleen, liver, and lung contained the largest amounts of iron, and also showed the widest variation. The high content of the liver and spleen is in agreement with the conception that these organs are the storehouses for this metal, the liver deriving most of its iron from ingested food and the spleen mainly from the hemoglobin of destroyed erythrocytes. The high content of the lung is due to the large amount of blood in the organ because of its vascularity and the presence of inflammatory processes in most cases of this series. The tissues containing moderate amounts of iron are heart, kidney, and tumor, whose content may be derived equally from the hemoglobin of the blood and from the tissue itself.

The pancreas, rib, thyroid, and bile are low in iron, and since there is very little blood in these organs most of their iron comes from the tissue itself.

Copper.—The copper content of the various tissues has very little relationship to the iron content. The liver and bile are highest in copper. The liver is the storehouse for copper, just as it is for iron, and as the bile has a high copper content the liver must act also as an excretory organ for copper. Kidney, heart, and pancreas have moderate amounts of copper; lung, tumor, thyroid, spleen, and rib a low content. In a comparison of the iron and copper content of the various tissues the outstanding contrast is that of the spleen. This tissue has the highest iron content, but on the other hand its copper content is one of the lowest.

Moisture.—The moisture content of the different tissues varies within a narrow range, tumor tissue being the highest except for bile. Bone contains the smallest amount of water. Liver and pancreas are low in moisture content because they contain large amounts of fat.

Table II: Distribution of Iron and Copper in Malignant Neoplastic Disease

Tissue	Percentage of H_2O					Mgm. Fe per 100 gm.					Mgm. Cu per 100 gm.				
	No. of autopsies	Maximum	Minimum	Mean	Probable error	No. of autopsies	Maximum	Minimum	Mean	Probable error	No. of autopsies	Maximum	Minimum	Mean	Probable error
Liver	42	88.0	68.0	77.3	0.33	42	427.0	21.6	119.3	7.83	42	8.15	0.72	2.85	0.163
Spleen	41	85.0	73.0	80.6	0.25	41	900.0	36.6	249.9	20.79	37	2.48	0.09	0.68	0.048
Kidney	39	87.3	78.5	82.7	0.22	39	86.4	14.2	37.4	1.65	39	3.10	0.36	1.32	0.067
Heart	38	85.9	77.2	80.9	0.23	38	89.2	3.8	32.1	1.70	37	2.68	0.40	1.31	0.061
Lung	34	87.1	74.0	82.9	0.37	33	232.0	29.8	102.1	5.05	34	3.41	0.15	0.87	0.071
Bile	27	98.0	64.2	84.3	1.04	23	40.8	3.2	12.8	1.28	20	24.9	0.22	3.71	0.787
Tumor	14	87.5	77.4	83.9	0.47	12	52.0	3.9	25.6	3.02	12	1.37	0.27	0.84	0.063
Pancreas	11	87.5	69.0	77.3	1.08	8	36.6	7.0	18.5	2.71	9	3.82	0.43	1.23	0.231
Thyroid	5	88.4	71.0	78.6	1.94	4	35.4	4.5	14.6	4.73	3	0.99	0.13	0.63	0.175
Rib	14	61.9	33.3	46.3	1.25	15	33.2	5.7	16.0	1.26	14	1.50	0.08	0.54	0.065

Table III: Distribution of Iron and Copper in Cases with Hemoglobin Less than 70 Per Cent

Tissue	Number	Percentage H_2O	Mgm. Fe per 100 gm.	Mgm. Cu per 100 gm.
Liver	10	77.9 ± 0.60	107.3 ± 16.64	3.09 ± 0.361
Spleen	8	80.8 ± 0.66	146.8 ± 14.51	0.77 ± 0.084 *
Kidney	9	83.8 ± 0.57	35.9 ± 3.05	1.95 ± 0.160
Heart	9	82.3 ± 0.51	37.5 ± 5.45	1.35 ± 0.111 *
Lung	9	83.0 ± 0.96	113.4 ± 11.19	0.79 ± 0.0845

* Values for copper are the means of 6 spleens and 8 hearts.

Anemia.—In Table I are reported 9 cases in which the hemoglobin was less than 70 per cent. These, together with No. 601, who suffered a severe hemorrhage shortly before death, were classed as anemic, and the means of the analyses are shown in Table III. Although some of the hemoglobin determinations and red cell counts were made days before death, a study of the case history indicated no change in the patient's condition that would lead to an improvement in the blood picture, but, rather, conditions suggested a progress of the anemia. Unfortunately, not enough cases in which the hemoglobin was above 70 per cent were obtained to form a normal group suitable for statistical comparison with the anemic group; in only 3 (Nos. 583, 645, and 679) were hemoglobin values obtained that would rule out an anemic condition at death. These cases, respectively, gave values of 61.2, 106.2, and 21.6 mgm. Fe, and 4.14, 3.52, and 1.84 mgm. Cu per 100 gm. in the liver; and 68.0, 154.0, and 76.0 mgm. Fe, and 0.86, 0.09, and 0.32 mgm. Cu per 100 gm. in the spleen. Except for the spleen of No. 645, all the iron values of the livers and spleens of the "normal" cases were lower than the means of the anemic group. The mean of the 3 values for copper in the livers (3.17 mgm. Cu per 100 gm.) was near the mean for the livers of the anemic group. For the spleens the mean (0.42 mgm. Cu per 100 gm.) was much less than the mean for the spleens of the anemic group.

Analyses of livers and spleens from cases of accidental death have been recorded in the literature as representing normal values for iron and copper. In an average of 5 cases Brückmann and Zondek (2) reported for liver 147.8 mgm. Fe, and in an average of 2 cases 2.8 mgm. Cu per 100 gm. For liver Sandberg and her associates (22) reported 44.7 mgm. Fe and 2.8 mgm. Cu per 100 gm. as averages of 15 cases. These values compare favorably with our so-called normal values except for the iron value of 147.8 mgm., which is near the mean of the iron in our anemic group. For spleen Sandberg reported as averages of 15 cases 137.2 mgm. Fe and 0.90 mgm. Cu per 100 gm. The means of our anemic group correspond more closely to these normals than to our so-called normal

values. In an anemic condition the reservoirs of iron and copper in the liver, and of iron in the spleen, might be depleted. Consideration of the results, however, shows that in these cases a lack of iron or copper is apparently not the factor in the production of the anemia.

Liver.—The liver has been analyzed for iron and copper more frequently than any other organ. Brückmann and Zondek, Sandberg and her group, and Schönheimer and Oshima (24) have all recorded analyses of the liver for both metals. Others have reported analyses for only copper: Chou and Adolph (4), Cunningham (5), Eggleton (7), Gerlach (11), Herkel (14), and Schönheimer and Herkel (23). Our mean value (Table II) for iron in the liver lies between the means reported by Brückmann and Zondek and Sandberg for normal liver, and our mean value for copper agrees with the means reported by Brückmann and Zondek and Sandberg for normal liver. Calculated on the basis of fresh weight, our mean values for liver are 26.9 mgm. Fe, and 0.64 mgm. Cu per 100 gm. Schönheimer and Oshima reported averages of 14 determinations for iron and 17 for copper in liver as 55.0 mgm. Fe and 0.248 mgm. Cu per 100 gm. fresh tissue. Gerlach, using a spectrographic technic, found in cancer a maximum of 1.9 mgm., a minimum of 0.4 mgm., and a mean of 1.05 mgm. Cu per 100 gm. of fresh liver. Sandberg recorded analyses of liver in over 100 cases of cancer without regard to the histology of the organ. The results showed a much wider range for both iron and copper than our analyses of 42 cases. Hahn and Fairman (12) reported copper contents of livers from 4 cases of malignant neoplastic disease, the average of which was 0.70 mgm. per 100 gm. of fresh tissue, comparing favorably with our mean of 0.64 mgm. Cu per 100 gm.

The cases were grouped according to sex, and the means and probable errors of the liver analyses calculated. The results are shown in Table IV. Males have a significantly higher moisture and iron content for the liver. Higher iron values would not be surprising, however, since blood hemoglobin values are higher for men than women. The increased moisture content may be due to the large number of congested livers and the few fatty livers in this group, while in the female group there are few congested livers and a larger number of fatty livers.

In Table V the livers are grouped according to histology. The livers in which no histological changes had taken place give a mean value for iron corresponding to that reported for normal livers by Sandberg and her associates, and a mean value for copper identical with those recorded by these authors and by Brückmann and Zondek. The mean value for moisture in the fatty livers is somewhat lower than the mean for livers that showed no histological change. The $\times$E value is 3.06.[3] The copper content of the livers with fibrosis is higher than that of the livers in this group showing no histological change. Several reports in the literature indicate that the copper content of cirrhotic livers is increased: Cherbuliez and Ansbacher (3), Herkel, and Schönheimer and Herkel.

TABLE IV: DISTRIBUTION OF IRON AND COPPER IN LIVERS ACCORDING TO SEX

Sex	Percentage H_2O	Mgm. Fe per 100 gm.	Mgm. Cu per 100 gm.
Males	78.5 ± 0.33	134.3 ± 10.94	2.94 ± 0.225
Females	75.2 ± 0.54	92.3 ± 8.10	2.67 ± 0.216
$\times$E *	5.22	3.08	0.87

* See footnote 3.

TABLE V: DISTRIBUTION OF IRON AND COPPER ACCORDING TO HISTOLOGY OF LIVER

Histology	Percentage H_2O	Mgm. Fe per 100 gm.	Mgm. Cu per 100 gm.
No change	77.4 ± 0.65	80.4 ± 19.12	2.83 ± 0.340
Congestion	78.4 ± 0.46	124.4 ± 8.80	2.47 ± 0.198
Fatty	74.4 ± 0.69	110.1 ± 12.25	2.39 ± 0.203
Fibrosis	78.3 ± 1.05	136.3 ± 14.56	5.83 ± 0.898

Spleen.—As for liver, most of the iron and copper values for spleen have been determined on individuals suffering from some disease: Chou and Adolph, Cunningham, Eggleton, Hahn and Fairman, Herkel, Tompsett (26), and Sandberg and her group. The only values available on normal spleen are in the report last cited, a mean of 137.2 mgm. Fe and 0.9 mgm. Cu per 100 gm. The values that they found in patients with cancer show a far greater range of variation than ours. Hahn and Fairman have reported the copper in the spleen from one case of myeloid leukemia as 0.29 mgm. Cu per 100 gm. fresh tissue. Our average value for spleen is 0.13 mgm. Cu per 100 gm. fresh tissue. Our value is lower than that reported by Sandberg for normal spleen, and corresponds more closely to the figure recorded by Eggleton (0.72 mgm. Cu per 100 gm.). For copper in the spleen all the values reported in the literature are within the range of values that we obtained. When the cases were tabulated according to sex no significant differences in the iron and copper contents

[3] $\times$ E indicates the number of times the difference of the two means exceeds the probable error of the difference of these two means.

of the spleen appeared (Table VI). Of the 41 spleens analyzed, 30 showed congestion but no significant difference could be found when this group was studied separately.

Kidney.—Brückmann and Zondek reported for normal kidney tissue values of 81.1 per cent moisture, 41.9 mgm. Fe, and 2.0 mgm. Cu per 100 gm. Our value for moisture is higher, while iron and copper are lower than these. Our mean of 39 cases is comparable to Eggleton's mean value of 1.41 mgm. Cu per 100 gm. obtained on 11 cases. The averages of 11

TABLE VI: DISTRIBUTION OF IRON AND COPPER IN SPLEENS ACCORDING TO SEX

Sex	Percentage H_2O	Mgm. Fe per 100 gm.	Mgm. Cu per 100 gm.
Males	81.1 ± 0.34	241.3 ± 25.04	0.70 ± 0.044
Females	79.8 ± 0.32	264.8 ± 37.64	0.65 ± 0.107

cases each reported by Tompsett and by Yagi (27) were similar to our mean of 0.23 mgm. Cu per 100 gm. fresh tissue. Since the great majority of the kidneys were nephritic no further statistical study was made of the iron and copper contents.

Aside from the reports by Brückmann and Zondek on liver and kidney and by Sandberg and her group on liver and spleen there are no other reports in the literature on the iron and copper contents of normal tissue. Although many workers believe that hospital autopsy material contains normal amounts of these metals, this conception is open to criticism since

TABLE VII: DISTRIBUTION OF IRON AND COPPER ACCORDING TO HISTOLOGY OF HEART

Histology	Percentage H_2O	Mgm. Fe per 100 gm.	Mgm. Cu per 100 gm.
No change	81.4 ± 0.45	36.6 ± 1.83	1.53 ± 0.116
Brown atrophy	81.2 ± 0.41	22.2 ± 2.60	1.04 ± 0.095
Fibrosis	80.1 ± 0.47	42.6 ± 6.14	1.44 ± 0.128
Fragmentation of muscle	78.7 ± 0.39	22.5 ± 0.97	0.93 ± 0.016

Sandberg pointed out that there may be an accumulation of iron and copper in severe chronic disease.

Heart.—The only values found in the literature for heart muscle were those given for copper in two reports. Chou and Adolph found an average of 3.64 mgm. Cu per 100 gm. for only 2 cases and Eggleton reported 1.34 mgm. Cu per 100 gm. as an average of 16 cases. Our mean of 37 analyses agrees with the latter. In 14 cases the heart muscle had undergone no histological change. Other cases were grouped according to the histological report, and compared statistically with the former group (Table VII). The two significant differences found in pathological conditions of the heart were in brown atrophy and fragmentation of the muscle fibers. The $\times E$ value was respectively 4.54 and 6.85 for iron and 3.27 and 5.40 for copper. The moisture content in the cases with fragmentation of the muscle was decidedly lower, the $\times E$ value being 4.54.

Lung.—Our mean value for copper in the lung is similar to that found by Eggleton in 10 cases (0.89 mgm. Cu per 100 gm.). In the great majority of cases inflammatory processes were in progress so no special statistical study could be made of the iron and copper. One case of anthracosis was found in which the iron content was 600.0 mgm. Fe per 100 gm. This was not included in the mean because the value was so much higher than the nearest value of 232.0 mgm. Fe per 100 gm. The high iron content of the lung compared with other tissues is undoubtedly due to the engorgement of this organ with blood.

Bile.—In bile obtained from the gall bladder at autopsy the copper varied more than the iron. In fact, the copper showed the widest variation of any of the material analyzed. The mean for iron was the lowest for all the material studied statistically. Our mean values for iron and copper, calculated on the basis of moist weight in order to compare them with the results of Judd and Dry (15), give 1.52 mgm. Fe and 0.44 mgm. Cu per 100 gm. Judd and Dry reported 11 cases, their average copper value agreeing with ours, but their iron (0.23 mgm. Fe per 100 gm.) being much lower.

Rib.—For rib the mean copper content of 12 cases, calculated on the basis of fresh weight, was 0.27 mgm. Cu per 100 gm., which is much lower than that found by Tompsett for 12 analyses (1.48 mgm. Cu per 100 gm. fresh tissue). Of the tissues studied statistically the rib gave the lowest value as well as the lowest mean value for copper.

Tumor.—Our values for moisture, iron, and copper in tumors are tabulated in Table VIII. The tumors were classified as sarcomas or carcinomas, and the means, together with the probable errors, calculated for each group. Because teratoma of the testicle contains both sarcomatous and carcinomatous elements in varying degrees, the two teratomas in this series were not classed in either group. The mean moisture content of tumors was higher than that of any other tissue examined. The sarcomas appeared to have a higher iron content than the carcinomas but the difference is not significant, the $\times E$ value being only 2.89, while we have always required a value greater than 3.00 to consider the difference significant. Tumors, in general, are not as vascular as most tissues. A small amount of blood in the tumor tissue would tend toward a low iron value. From the results of our analyses we have classed tumors in the group of tissues having a moderate iron content. However, one

specimen, a metastasis from a teratoma of the testicle, was extremely hemorrhagic and gave a value of 122.0 mgm. Fe per 100 gm. Because this was more than twice the next highest value we did not include this in the mean value of all the tumors. The two teratomas of the testicle gave the highest iron values of any of the neoplasms analyzed. Because, macroscopically, one was extremely hemorrhagic and the other also contained more blood than any of the other tumors, the increased iron may have come from blood. It is impossible without further data, therefore, to conclude that the high iron values are characteristic of this type of tumor. The copper content of the teratomas was not increased. Dutoit and Zbinden (6) failed to detect copper in tumors by means of the spectrograph. Gerlach, using spectrographic technic, analyzed 16 malignant growths, which varied from 0.05 to 2.0 mgm. Cu per 100 gm. fresh tissue, with a mean of 0.53 mgm. Hahn and Fairman reported the copper content of a melanoma of the liver as 0.45 mgm. Cu per 100 gm. fresh tissue. Rosenthal (21) recorded the copper content of a primary carcinoma of the liver as 1.5 mgm. Cu per 100 gm. fresh tissue. Our range of values for copper in tumors is much narrower than that of Gerlach, owing, perhaps, to the difference in methods used.

Pancreas.—Our mean value for copper in the pancreas, calculated on the basis of fresh tissue, is 0.30 mgm. Cu per 100 gm., compared with the value of 0.227 mgm. Cu per 100 gm. reported by Tompsett for 11 cases. Eggleton's mean value in 13 cases was 0.87 mgm. Cu per 100 gm. With a maximum of 1.42 and a minimum of 0.41 mgm. Cu per 100 gm., his values covered a narrower range than ours.

Thyroid.—In the literature there are only two reports of analyses on the thyroid gland. Sheldon and Ramage (25), using the spectrographic method of analysis, reported the presence of iron and copper in thyroid tissue. Herkel found 0.14 mgm. Cu per 100 gm. fresh tissue in an analysis of one thyroid. This compares favorably with our mean of 0.10 mgm. Cu per 100 gm. fresh tissue. Compared with other tissues studied statistically, thyroid has a low content of both iron and copper.

TABLE VIII: DISTRIBUTION OF IRON AND COPPER IN TUMORS

Autopsy No.	Diagnosis	Percentage H_2O	Mgm. Fe per 100 gm.	Mgm. Cu per 100 gm.
683	Fibroid, uterus	81.5	3.9	1.37
678	Teratoma, testicle	87.5	52.0	0.77
602	" "	84.2	122.0 *	0.64
	CARCINOMAS			
601	Epithelioma, larynx	86.4	32.0	1.14
675	Carcinoma, lung	87.0	10.4	0.47
685	Epithelioma, tonsil	83.0	32.5	
680	Carcinoma, prostate	81.4	18.4	0.27
665	" breast	84.8	17.6	0.76
744	" stomach	77.4	6.0	
	Mean	83.3 ± 0.99	19.5 ± 3.01	0.66 ± 0.127
	SARCOMAS			
591	Sarcoma, kidney	83.2		0.85
588	Lymphoblastoma	86.3	29.4	1.16
646	Hodgkin's sarcoma	83.6	33.3	0.96
583	Lymphosarcoma	83.6	22.4	0.79
672	Sarcoma, pancreas	84.8	49.6	0.94
	Mean	84.3 ± 0.38	33.7 ± 3.89	0.94 ± 0.042
	Mean, all tumors	83.9 ± 0.47	25.6 ± 3.02 *	0.84 ± 0.063

* Iron value of 122.0 mgm. not included in mean value of all tumors.

Miscellany.—In Table IX are the results of analyses on a miscellaneous collection of tissues. In two cases, adrenals and skin, not enough material was available for copper analyses. Schönheimer and Oshima reported analyses of gallstones from 6 cases. Their results for iron gave as a maximum, 237 mgm.; as a minimum, 43.8 mgm.; and as a mean, 143.3 mgm. Fe per 100 gm. For copper the maximum was 207 mgm.; the minimum, 18.0 mgm.; and the mean, 86.8 mgm. Cu per 100 gm. fresh tissue. Our results are much lower. A wide variation, however, is not unexpected since we found wide limits for the iron and copper of bile. Sheldon and Ramage found both iron and copper in the adrenals spectrographically. Bodansky

TABLE IX: IRON AND COPPER IN SINGLE SPECIMENS OF MISCELLANEOUS MATERIAL

Autopsy No.	Material	Percentage H_2O	Mgm. Fe per 100 gm. tissue		Mgm. Cu per 100 gm. tissue	
			Dry weight	Fresh weight	Dry weight	Fresh weight
680	Gallstones			1.5		0.38
691	"			4.3		24.5
662	Adrenals	82.2	25.0			
688	Cerebrum	81.1	17.4	3.3	2.25	0.43
688	Cerebellum	79.4	17.9	3.7	1.53	0.31
Leg amputation	Muscle	72.0	12.7		0.09	
	Skin	53.5	4.1			
	Bone	25.7	2.3		0.88	

(1) recorded, in 4 analyses of brain tissue, between 0.36 and 0.60 mgm. Cu per 100 gm. fresh tissue. Eggleton described 17 analyses of brain tissue; for cerebrum he obtained values between 1.42 and 2.47, and for cerebellum 0.82 and 4.88 mgm. Cu per 100 gm. Our values are within the range of those found by both Eggleton and Bodansky. From a leg amputated for Ewing's tumor of the tibia samples of normal skin, muscle, and bone were removed for analyses. The value for copper in muscle was the lowest of any tissue analyzed, agreeing with the value of 0.18 mgm. Cu per 100 gm. obtained by Kleinmann and Klinke (17), but lower than Eggleton's average of 9 analyses, 0.64 mgm. Cu per 100 gm., and Chou and Adolph's mean of two analyses, 1.26 mgm. Cu per 100 gm. The iron content of skin was one of the lowest of any tissue analyzed. In the bones of the foot both the iron and copper were low; the iron content, indeed, was the lowest of any tissue analyzed, even much lower than the lowest value obtained for rib.

SUMMARY

The moisture, iron, and copper content of various tissues and of bile from 43 cases of malignant diseases is reported. The moisture content varied little, tumor being the highest. The material can be arranged in decreasing order of iron content: *high,* spleen, liver, and lung; *intermediate,* kidney, heart, and tumor; *low,* pancreas, rib, thyroid, and bile; or in decreasing order of copper content: *high,* bile and liver; *intermediate,* kidney, heart, and pancreas; *low,* lung, tumor, spleen, thyroid, and rib. Differences in moisture, iron, and copper could be correlated with certain histological changes.

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Abstracts

Experimental Research, Animal Tumors

Der Metallkrebs. Ein neues Prinzip der Krebserzeugung. [Metal Cancer: A New Principle in Carcinogenesis.] SCHINZ, H. R. *Schweiz. med. Wchnschr.*, **72**:1070-1074. 1942.

From 1934 to 1936, inclusive, amounts of 0.1 to 0.15 gm. of chromium, arsenic, or cobalt were deposited in the marrow cavity of the femur in rabbits. Among 21 survivors of an epidemic no tumors were found 3 years later. For one reason or another connected with the war 9 of these animals disappeared, but of the remaining 12, 7 developed carcinomas or sarcomas after $3\frac{1}{2}$ years or more, some at the site of the metal depot, others at a remote site (lungs). Some of the growths metastasized.

The author suggests that the metals must have been slowly distributed throughout the body, where they became active in traces.

A full report is promised, as well as a resumption of the investigation when favorable conditions are restored.—W. H. W.

A Developing Factor in Experimental Blastogenesis. MOTTRAM, J. C. [Mount Vernon Hosp., and Radium Inst., London, England] *J. Path. & Bact.*, **56**:181-187. 1944.

Experiments are described of the following type: 3,4-benzpyrene in acetone was applied three times on alternate days to both flanks of a mouse; subsequently acetone was applied to the left side and croton oil in acetone to the right side. After 20 weeks, there were 5 tumors, one malignant, on the right, and none on the left side. Application of croton oil before benzpyrene also promotes the development of tumors. The author discusses (1) the results of earlier workers, (2) the part played by hyperplasia and chronic irritation in the genesis of cancer, and (3) the statistical value of comparative experiments on both sides of the same mouse ". . . . blastogenic agents are likely to be missed unless a developing agent is applied at the same time. . . . . The combination of croton oil with benzpyrene provides a much more delicate test than the sledge-hammer treatment of continuous painting."—E. L. K.

Effect of Two Azo Compounds When Added to the Diet of Mice. ANDERVONT, H. B., WHITE, J., and EDWARDS, J. E. [National Cancer Inst., Bethesda, Md.] *J. Nat. Cancer Inst.*, **4**:583-586. 1944.

Diets containing *o*-aminoazotoluene and *p*-dimethylaminoazobenzene were fed to strain C mice of both sexes. The former induced many hepatic changes, hepatomas, pulmonary tumors, and hemangioendotheliomas, whereas the latter induced only a few hepatic reactions and few hepatomas. Female mice were more susceptible than males to hepatic reactions, hepatomas, and hemangioendotheliomas induced with *o*-aminoazotoluene. When orally administered, this compound elicited many pulmonary hemangioendotheliomas.—Authors' summary.

Administration of 3,5-Cholestadiene and Dicholesteryl Ether to Mice and Rats. LARSEN, C. D., and BARRETT, M. K. [National Cancer Inst., Bethesda, Md.] *J. Nat. Cancer Inst.*, **4**:587-594. 1944.

Three groups of rats were fed diets containing 3,5-cholestadiene at graded levels. No characteristic pathology of gastric or hepatic tissues, which would distinguish one experimental group from another or from the controls, was noted. Hyperkeratosis of the forestomach was rather evenly distributed among all the groups. No papillomas were found in the stomachs of the control rats, whereas 1, 1, and 3 were found in the forestomachs of rats fed the low, intermediate, and high concentrations of the hydrocarbon, respectively.

The highest level of ingested hydrocarbon appeared to exert a low-grade systemic toxicity characterized by loss in weight of the rats; all animals in this group were dead after 8 months. The animals maintained on the diet containing the intermediate level of 3,5-cholestadiene exhibited a similar reaction, but to a much lesser degree.

Pellets of 3,5-cholestadiene, when implanted subcutaneously in Wistar rats and in strain C3H mice, were inert. Autopsies up to 16 months after implantation revealed intact pellets and no evidence of hyperplasia in adjacent tissues.

Dicholesteryl ether, implanted subcutaneously in strain C3H mice in the form of pellets, remained intact and caused no tissue reaction.

3,5-Cholestadiene, administered orally or subcutaneously, presented no evidence of carcinogenicity in these experiments.—Authors' summary.

Test of Desoxycholic Acid for Carcinogenicity in Rats and Mice. BARRETT, M. K., and LARSEN, C. D. [National Cancer Inst., Bethesda, Md.] *J. Nat. Cancer Inst.*, **4**:595-600. 1944.

Three groups of rats were fed diets containing desoxycholic acid at graded levels for as long as 20 months without evidence of toxic effects. No characteristic pathological picture, which would distinguish one experimental group from another or from the controls, was noted in the gastric tissues.

Pellets of desoxycholic acid, implanted subcutaneously in rats, incited a temporary local tissue reaction, which subsided within 2 weeks. Autopsy of 41 animals after 13 to 16 months revealed neither gross nor microscopic evidence of neoplasia or hyperplasia. Subcutaneous implantation of pellets consisting of equal parts of the acid and cholesterol likewise led to negative results as far as tumor genesis was concerned.

Subcutaneous implantation of desoxycholic acid pellets in 46 strain C3H mice led to necrosis, sequestration, and sloughing of the pellet in most cases. Twenty-six mice that survived for 6 months showed no evidence of hyper-

plasia at the pellet site. Similar implantation of acid-cholesterol pellets was followed by sloughing in about half the mice. Pellets that were retained in the remainder of the mice appeared to be completely absorbed within 35 days. These mice, autopsied 8 months later, showed no reaction at the pellet site.

Desoxycholic acid, as administered in these experiments, showed no evidence of carcinogenicity.—Authors' summary.

The Inhibition of Enzyme Systems by Metabolic Products of Carcinogenic Compounds. Urease and Succinoxidase. Elson, L. A., and Hoch-Ligeti, C. [Royal Cancer Hosp. (Free), London, England] *Biochem. J.*, **38**:x. 1944.

When azobenzene is given to rats benzidine can be isolated from the urine (Elson and Warren), and evidence has been obtained that *p*-dimethylaminoazobenzene undergoes a similar rearrangement to 2,4-diamino-5-dimethylaminodiphenyl. Both these products have a strong inhibitory action on urease and succinoxidase systems. *p*-Phenylenediamine and dimethyl-*p*-phenylenediamine on oxidation give products that inhibit the succinoxidase system; the rate of oxidation of the diamines seems to be related to the amount of cytochrome *c* present. When the diamines are added to the complete system the rate of oxygen uptake is first increased, presumably due to the oxidation of the diamine by the cytochrome, and then inhibited, often completely.—E. L. K.

Comparative Glycolytic and Respiratory Metabolism of Homologous Normal, Benign, and Malignant Rabbit Tissues. With Particular Reference to the Benign Virus Papilloma (Shope) and a Transplanted Cancer Derived Therefrom (the V2 Carcinoma). Kidd, J. G., Winzler, R. J., and Burk, D. [Rockefeller Inst. for Med. Research, New York, N. Y., and National Cancer Inst., Bethesda, Md.] *Cancer Research*, **4**:547-553. 1944.

The data indicate that the cells of the V2 rabbit carcinoma possess a glycolyzing capacity which, calculated on a dry weight basis, is about as great as that of the cells of 2 other transplanted rabbit cancers (the Brown-Pearce carcinoma and sarcoma I of Andrewes and Ahlström), and is considerably greater than that of the benign papilloma cells of the sort from which they originally derived. The derived metabolic quotients, which relate glycolysis to oxygen consumption independently of dry weight, lend further support to the view that the metabolism of the V2 carcinoma cells is characteristic of malignant cells generally, whereas that of the Shope virus papilloma is characteristic of benign tumor cells and distinguishable in certain respects from that of normal rabbit skin cells. The differences in metabolism between the benign papilloma cells and the homologous V2 carcinoma cells are the more noteworthy since the former proliferate quite as rapidly as the latter. It remains to be ascertained whether the metabolic differences have something to do with the differences in the form and behavior of the papilloma and carcinoma cells, with the failure of repeated attempts to procure a causative virus from the V2 carcinoma, or with antigenic differences in the sedimentable constituents of the two sorts of cells.—Authors' abstract.

The Treatment of Postoperative Hypoproteinemia in Patients with Cancer of the Colon and Rectum. Binkley, G. E., Abels, J. C., and Rhoads, C. P. [Memorial Hosp., New York, N. Y.] *Ann. Surg.*, **117**:748-753. 1943.

In 23 (36%) of 65 patients with cancer of the colon and rectum hypoproteinemia, as determined by the falling-drop method, was present. The number of patients with serum proteins below 6.5 gm. per cent increased to 86% during the first postoperative week. Whole blood, where there was associated anemia, and plasma were used to combat this condition in the early stages, and later dietary nitrogen was effective. In all but 1 of 14 of the cases the serum protein levels were higher from 20 to 150 days after the parenteral injection of protein than during the first postoperative week. It was more difficult to combat hypoproteinemia in cases where there were infections.—W. J. B.

Metabolic Studies on Patients with Cancer of the Gastrointestinal Tract. XIV. The Effects of High Protein Diets on the Prevention of Postoperative Hypoproteinemia in Patients with Gastric Cancer. Rasmussen, L. H., Abels, J. C., Pack, G. T., and Rhoads, C. P. [Memorial Hosp., New York, N. Y.] *J. A. M. A.*, **124**:358-360. 1944.

In patients with gastrointestinal cancer, the development of significant postoperative hypoproteinemia is an almost uniform finding. The condition is the result of numerous factors including the disease itself, poor liver function, and reduced protein intake following resection of some portion of the alimentary tract. The preoperative ingestion of considerable amounts of protein for from 10 to 22 days prevents the development of serious degrees of hypoproteinemia in patients with gastric cancer during their postoperative periods of negative nitrogen balance. These conclusions are the result of nitrogen balance studies on 6 patients with carcinoma of the stomach, receiving diets containing 101 to 196 gm. of protein daily.—M. E. H.

Metabolic Studies in Patients with Cancer of Gastro-Intestinal Tract. XV. Lipotropic Properties of Inositol. Abels, J. C., Kupel, C. W., Pack, G. T., and Rhoads, C. P. [Memorial Hosp., New York, N. Y.] *Proc. Soc. Exper. Biol. & Med.*, **54**:157-158. 1943.

From previous studies it appears that the liver of patients with gastrointestinal cancer is infiltrated with fat, but in 11 patients who received 8 gm. of lipocaic before laparotomy the fat content was found to be normal. Since lipocaic contains relatively large amounts of choline and inositol, each of which is lipotropic, the effect of these substances was tested separately.

Supplement of either 8 gm. lipocaic, 3 gm. choline chloride, or 1.2 gm. inositol was found to correspond to a reduction of hepatic lipid of 51, 39, and 58% respectively. A reduction of 50% lipid was observed when 0.28 gm. inositol was administered 10 hours before intervention. Since this amount is equal to the quantity of inositol present in an effective dose of lipocaic, it is suggested that inositol alone may account for the lipotropic properties of the crude preparation.—M. B.

Metabolic Studies of Patients with Cancer of the Gastrointestinal Tract. XVI. The Treatment of Hypochloremia Refractory to the Administration of Sodium Chloride, Especially in Patients with Gastrointestinal Cancer. Ariel, I., Abels, J. C., Pack, G. T., and Rhoads, C. P. [Memorial Hosp., New York, N. Y.] *J. A. M. A.*, **123**:28-30. 1943.

Five patients showing postoperative hypochloremia resistant to the administration of large amounts of saline solution were found to have an associated hypoproteinemia. In those instances in which the level of serum protein was increased therapeutically, the disturbed electrolyte equilibrium was corrected. The existence of hypoproteinemia may seriously prevent the correction of the chloride imbalance by the administration of saline solution alone.—M. E. H.

Metabolic Abnormalities in Patients with Cancer of the Gastrointestinal Tract. A Review of Recent Studies. Abels, J. C., Ariel, I., Rekers, P. E., Pack, G. T., and Rhoads, C. P. [Memorial Hosp., New York, N. Y.] *Arch. Surg.*, **46**:844-860. 1943.

Patients with gastrointestinal cancer have low levels of plasma vitamin A not explainable by inadequate ingestion, or poor absorption of the vitamin, or by inability of the liver to store vitamin A. The administration of yeast, lipocaic, or choline raised the plasma vitamin A levels in these patients although the mechanism involved is not clear.

Fifty-nine per cent of patients with gastric cancer suffer from hypoproteinemia. This is not because of dietary deficiency or excess bleeding but more likely is the result of metabolic abnormality that interferes with the maintenance and replacement of serum albumin, possibly hepatic dysfunction.

Patients with cancer of the gastrointestinal tract have a high incidence of hepatic dysfunction as indicated by diminished ability of the liver to synthesize, store, conjugate, and excrete metabolites.

Postoperative metabolic abnormalities include the following: (1) Absorption of fat after total gastrectomy is low, and the steatorrhea is apparently related to the dietary content of fat and possibly of protein and to the fat-splitting pancreatic enzymes. (2) Hypoprothrombinemia is frequent in patients with gastrointestinal cancer and may persist for months in those from whom the cancer is removed. (3) Postoperative anemia of mild degree may persist in patients whose gastrointestinal neoplasms have been removed, although the degree of anemia is less than in those still bearing tumors.—W. A. B.

Abnormal Alpha Ketosteroid Excretion in Patients with Neoplastic Disease. Dobriner, K., Rhoads, C. P., Lieberman, S., Hill, B. R., and Fieser, L. F. [Memorial Hosp., New York, N. Y., and Converse Memorial Lab., Harvard Univ., Cambridge, Mass.] *Science*, **99**:494-496. 1944.

Fractionation of α-ketosteroid extracts of urines from patients with neoplastic diseases yielded several homogeneous substances some of which were not obtained from normal persons or from those with certain nonneoplastic disorders.

An analysis of the relative amounts of these substances gave distribution patterns that were definitely abnormal for patients with lymphatic leukemia and cancer, while the pattern obtained from a patient with myeloid leukemia was very similar to the pattern for normal persons.—R. B.

Experimentelle Untersuchungen über Krebserzeugung durch Photosensibilisierung. [Experimental Investigation on Carcinogenesis through Photosensitization.] Miescher, G. [Dermatologischen Universitätsklinik Zürich, Zurich, Switzerland] *Schweiz. med. Wchnschr.*, **72**:1082-1084. 1942.

Only one among several investigators has found that photosensitizing agents such as hematophorphyrin or eosin increase the activity of carcinogens.

In an attempt to settle this question the author exposed mice sensitized with anthracene, which is not carcinogenic, to light from which the ultraviolet and heat rays had been filtered out.

No tumors appeared, and the conclusion is drawn that even a strong and long-continued photodynamic reaction in the skin can be of little significance in carcinogenesis.

In the one positive result mentioned in the opening paragraph photosensitization facilitated carcinogenesis in some non-specific manner. In any case, there is no warrant at present for regarding photosensitization as a new and specific carcinogen.—W. H. W.

La cancérisation artificielle en atmosphères différemment ionisées. [The Development and Growth of Tumors in Air Variously Ionized.] Joyet, G. [Centre Anticancéreux Romand, Service des Recherches Expérimentales, Lausanne, Switzerland] *Schweiz. med. Wchnschr.*, **72**:1077-1078. 1942.

Transplanted tumors grew and benzpyrene carcinomas developed in rats and mice kept in an atmosphere ionized with various preparations of radium as they did in the controls.

Though the experiments are not yet finished they give no support so far to the suggestion of several authors that the ions of the atmosphere are concerned in carcinogenesis.—W. H. W.

Growth Rate and Development of Tumors Induced with Ultraviolet Radiation. Blum, H. F. [National Cancer Inst., Bethesda, Md.] *J. Nat. Cancer Inst.*, **4**:559-569. 1944.

Measurements of growth rates of tumors induced with ultraviolet radiation are described. The growth rates of the gross tumors are not correlated with the time required for their appearance but are the same for early and late appearing tumors. The growth rates are not correlated with the age of the animals, nor with the recency of exposure to ultraviolet radiation. Estimates based on individual tumors show that the growth rate does not remain constant throughout development and does not follow the same pattern in all tumors of the same type. Experiments to determine the effect of interruption of the schedule of exposures on development time suggest that opposing growth and regressive processes determine the time at which a tumor becomes established so that it may continue to grow. The general evidence indicates that the tumor cells do not escape and assume their own essential proliferation rates, but that rates of tumor growth are to a great extent dominated by the controlling influence of the tissues.—Author's summary.

Influence of Environment on Mammary Cancer in Mice. ANDERVONT, H. B. [National Cancer Inst., Bethesda, Md.] *J. Nat. Cancer Inst.,* **4**:579-581. 1944.

Both virgin and breeding female C3H mice developed mammary tumors earlier when kept segregated, 1 mouse to a cage, than they did when living together, 8 to a cage.

Vaginal smears taken from virgin mice indicated that estrous cycles in the segregated animals occurred earlier, were more frequent, and lasted longer than they did in nonsegregated animals. Thus, hormonal stimulation was presumably greater in the segregated mice and could account for the earlier development of tumors amongst them.—R. B.

Observations on Mouse Tumors Cultivated in the Yolk Sac of the Embryonic Chick. HEILMAN, F. R., and BITTNER, J. J. [Mayo Clinic, and Univ. of Minnesota Med. Sch., Rochester, Minn.] *Cancer Research,* **4**:578-582. 1944.

Spontaneous mammary carcinoma from mice of the A and C3H stocks were tested in chick embryos. The A tumor gave large growths following the primary inoculation, but the second or third yolk-sac transfer resulted in the death of the embryos after 3 to 6 days. One mammary carcinoma from a C3H female was implanted in eggs after 13 passages in mice. During the early serial yolk-sac passage the tumor was transferred at 12-day intervals, but after the eighth serial passage the tumor had to be transferred at shorter and shorter periods because of the death of the embryos. The tumor was lost in the 20th passage owing to the death of the embryos on the night of the seventh day. The increasing mortality rate of the embryos was not related to the size of the tumor.

Following the fifth serial passage in eggs the C3H mouse tumor was inoculated into mice. It grew progressively in mice of the C3H stock and their hybrids but did not give temporary growth in mice of the A stock. Following the 11th serial passage in eggs, the C3H stock tumor gave temporary growth in 44 of 50 mice of the C57 black, C, A, and dilute brown (sublines 212 and 12) stock; 3 mice of the 212 line of the dilute brown stock showed progressive growth. After the regression of their tumors, the mice were resistant to reinoculation. These data suggested that the genetic constitution of the mouse tumor had changed during serial passage in chick embryos.

A limited number of attempts to find a cell-free agent in the yolk from tumor-bearing eggs that would produce tumors in mice within a few days resulted in failure. Material for injection was obtained by means of the following technics: filtration through Berkefeld N candles; rapid freezing and thawing; use of supernatant from an ether suspension; and centrifugation of the blood and allantoic fluid from embryos with tumors.

When untreated and unfiltered yolk surrounding large tumors was injected into mice, tumor resulted within 10 to 30 days in 6 of the 8 mice tested, which suggested the transfer of living tumor cells.—Authors' abstract.

La colchicine dans le traitement du cancer de la souris. [Colchicine Treatment of Mouse Cancer.] NICOD, J. L., and REGAMEY, J. *Schweiz. med. Wchnschr.,* **72**: 1074-1077. 1942.

Among 143 mice with benzpyrene carcinomas of the skin, or spontaneous mammary carcinomas, treated with modifications of the mixture of powdered organs suggested by Vlès and de Coulon (Proc. II. Internat. Cancer Congr., 1936) the tumor was inhibited, or made to disappear, in 12 and 13% respectively.

Among 114 mice that received injections or inunctions of colchicine in addition, the inhibition was evident in 23 and 28%.

Except in those few cases where the tumors disappeared life was not prolonged, and there is no reason, therefore, to hope that the treatment might be of practical value.—W. H. W.

Mitosenschädigung und Hormonwirksamkeit bei Steroiden. [Mitotic Damage and the Hormonal Activity of Steroids.] MÖLLENDORF, W. v. [Zurich, Switzerland] *Schweiz. med. Wchnschr.,* **72**:1021. 1942.

Certain steroids caused mitotic anomalies in tissue cultures, and growth disturbances that seemed to be related to the mitotic anomalies in malignant new growths—W. H. W.

Chromosome Size in Normal Rat Organs in Relation to B Vitamins, Ribonucleic Acid, and Nuclear Volume. BIESELE, J. J. [Univ. of Pennsylvania, Philadelphia, Pa.] *Cancer Research,* **4**:529-539. 1944.

Chromosome sizes in normal rat organs vary to some extent with nuclear volume, but they do not form a polymeric series by progressively doubling in volume from one tissue to another. The changes in chromosome volume are small, although often significant, and are not accompanied by changes in the number of plasmosomes carried by the diploid set of chromosomes. Since the average chromosome volume of normal rat organs does not vary in accordance with the cytoplasmic concentration of ribonucleic acid nor with the development of heterochromatin and plasmosomes, differences in chromosome size are probably not determined by differences in the quantity of polynucleotides on the chromosomes. However, the average chromosome volume is directly proportional to the total concentration of B vitamins, with the exception of inositol, reported in the literature. It is proposed that the difference in chromosome size from one normal cell type to another in rats depends on the development and activity of the euchromatin in synthesizing the protein parts of intracellular enzymes. Hence the greater the development of the euchromatin, *i.e.,* the larger the chromosomes, the greater is the bound vitamin capacity of the organ.—Author's abstract.

Size and Synthetic Activity of the Chromosomes of Two Rat Neoplasms. BIESELE, J. J. [Univ. of Pennsylvania, Philadelphia, Pa.] *Cancer Research,* **4**:540-546. 1944.

Chromosomes in hepatoma 31 and Walker carcinosarcoma 256 are of 3 sizes: small ones of about the size found in newborn rats or in adult organs poor in B vitamins; chromosomes about twice as large, that are in the majority; and chromosomes about 4 times as large. The chromosomes of double and quadruple size in the 2 cancers are probably composed of more discrete strands

than are chromosomes of normal tissues, since in the tumors the proportion of division figures that are polyploid is greatly exceeded by the proportion of resting nuclei with more plasmosomes than are carried by the diploid set of normal chromosomes. Most of the hepatoma chromosomes are double the size of newborn or perhaps fetal rat liver chromosomes rather than double the volume of actively functioning adult liver chromosomes.

Because of the double nature of most of the cancer chromosomes, one-half their average volume is to be used in assessing their synthetic activity. On this basis the two tumors should have a low over-all rate of synthesis of chromosomal products, and this is made probable by evidence from the literature of low B vitamin content, low activity of a number of enzymes, and a decrease in certain metals in these and other cancers.—Author's abstract.

Production of Malignancy In Vitro. VIII. Observations on the Mitochondria and Golgi Material. Dalton, A. J., and Earle, W. R. [National Cancer Inst., Bethesda, Md.] *J. Nat. Cancer Inst.*, **4**:539-554. 1944.

Mitochondria and Golgi material were demonstrated in both carcinogen-treated and control cultures of mouse fibroblasts, with no differences between them that could be related to the process of malignant transformation *in vitro*. However, the orientation of the Golgi material was found to be correlated with the growth pattern of cultures treated with the carcinogen for different lengths of time, being located distally (toward the periphery of the cultures) more frequently in cells of the faster growing cultures.

Studies of mitochondria in (1) tumors arising in mice from implants of carcinogen-treated cultures, (2) transplants of spontaneous fibrosarcomas, and (3) normal fibroblasts, revealed no differences associated with malignancy; but the Golgi material was hypertrophied in both types of tumors and in the endothelial cells of host blood vessels supplying them, compared with its condition in normal fibroblasts.—R. B.

Ciliated Cells of the Thyroid of the Mouse. Dunn, T. B. [National Cancer Inst., Bethesda, Md.] *J. Nat. Cancer Inst.*, **4**:555-557. 1944.

Ciliated cells were found in histologic sections of the thyroids of C3H and A strain mice. Ten of 22 C3H mice 10 months of age, and 5 of 25 A mice of the same age had some of the ciliated thyroid cells. None of these cells were found amongst 5 strain A mice, 11 weeks old, but a number of them were present in the thyroids of 10 newborn C3H mice.—R. B.

Injection and Clearing Method for the Rabbit's Ear. Dunn, T. B., and Kessel, A. M. [National Cancer Inst., Bethesda, Md.] *J. Nat. Cancer Inst.*, **4**:359-360. 1944.

A method for use in the study of vascular structure.

Clinical and Pathological Reports

Etiology

Karzinom und Entzündung im Rahmen allgemeinbiologischen Geschehens. Der Versuch einer Synthese. [Carcinoma and Inflammation from the Standpoint of General Biology. Attempt at a Synthesis.] Hass, E., Leipzig: J. A. Barth. Tübingen. pp. 96. 1942. Reviewed in *Schweiz. med. Wchnschr.*, **72**:803. 1942.

A highly philosophical discussion of etiology.—W. H. W.

Grundsätzliches über den Krebs in unserer Armee. [Cancer in the Swiss Army.] Meyenburg, H. v. [Universität Zürich, Zurich, Switzerland] *Schweiz. med. Wchnschr.*, **72**:1079-1081. 1942.

It is highly improbable that there is anything in military service that predisposes to cancer. The author finds no evidence that bodily exertion has any influence on the growth of a malignant tumor. The question whether a malignant growth was present at the time of enlistment, or developed later, cannot be answered, because the latent period is unknown.—W. H. W.

Radiation—Diagnosis and Therapy

A Review of the Gastro-Enterologic Diagnostic Roentgenologic Literature for the Year 1942. Rigos, F. J., and Kirklin, B. R. [Mayo Clinic, Rochester, Minn.] *Gastroenterology*, **1**:942-960. 1943.

The article is a fairly comprehensive survey of all leading American papers on the subject. The bibliography includes 126 titles. Since the paper is a digest of other articles, the original should be consulted.—A. C.

Three and One-Half Years' Experience with the 1,000 Kilovolt Roentgen Therapy Unit at Memorial Hospital. Hocker, A. F., and Guttman, R. J. [Memorial Hosp., New York, N. Y.] *Am. J. Roentgenol.*, **51**:83-94. 1944.

The results of treatment with million volt x-rays of 315 cancer patients are tabulated. Of the total number 213 are dead. Of these, 145 were in a very advanced stage of the disease and were treated palliatively; many of the others presented more complicated problems than usually seen in the radiation therapy patient. However, in those who died, considerable palliation was obtained. Survival rates even on the living group are not a fair indication of the value of million-volt therapy, because, as is usually the case when a new method of treatment is employed, the majority of the first patients were in advanced stages of the disease. An analysis is made of factors which should determine what types of cancer might be expected to present better results with million volt than with 200 kilovolt therapy.—E. H. Q.

The Treatment of Accessible Malignant Tumors with Short Distance Low Voltage Roentgen Rays. Smithers, D. W. [Royal Cancer Hosp., London, England] *Am. J. Roentgenol.*, **51**:730-738. 1944.

A review is presented of 466 cases of malignant disease and 294 of non-malignant, treated by 40-60 kv. x-rays, at target skin distances of 2 to 10 cm. Depth dose and isodose charts are given for various voltage-filter-distance combinations. Practical methods for shielding eyes and other normal parts are discussed.—E. H. Q.

Brocq-Belot's Technique in the Treatment of Superficial Skin Cancers. Brodeur, P. [Ottawa General Hosp., Ottawa, Canada] *Canad. M. A. J.*, **49**:109-110. 1943.

The paper reports on the apparent cure of 22 epidermoid carcinomas and 10 basal cell carcinomas treated by the Brocq-Belot technic.—A. C.

Radium Therapy in the Treatment of Cancer of the Skin. Piatt, L. M. [Columbus, Ohio] *J. Oklahoma M. A.*, **36**:415-417. 1943.

It is maintained that satisfactory therapeutic, and good cosmetic, results can be obtained by radium implantation. The paper is chiefly concerned with details of technic.—E. E. S.

Brain Tumors in the Presence of Normal Air Studies. Poppen, J. L., and Peacher, W. G. [Lahey Clinic, Boston, Mass.] *Surg. Clin. North Am.*, **23**:803-813. 1943.

A report of 10 cases, demonstrating that visualization of the ventricular system is not always diagnostic even in the presence of tumors producing physical signs and symptoms.—J. L. M.

The Encephalographic Appearance in Two Cases of Pontine Glioma in Children. Gardner, W. J., and Shannon, E. W. [Cleveland Clinic, Cleveland, Ohio] *Am. J. Roentgenol.*, **51**:697-698. 1944.

Two case reports are presented, with radiographs and photographs of autopsy specimens.—E. H. Q.

Spontaneous Rib Fractures Following Irradiation for Cancer of the Breast. Friedmann, A. B. [Kings County Hosp., Brooklyn, N. Y.] *Am. J. Roentgenol.*, **50**:797-800. 1943.

A case report.—E. H. Q.

Regression of Bone Metastases from Breast Cancer after Ovarian Sterilization. Ritvo, M., and Peterson, O. S., Jr. [Pondville Hosp., Walpole, Mass.] *Am. J. Roentgenol.*, **51**:220-229. 1944.

Roentgen sterilization is advocated for all patients with bone metastases from cancer of the breast. The withdrawal of ovarian hormone results in relief of pain, improvement in general condition, and sometimes regression or disappearance of the metastases. The procedure is not recommended for patients with cancer of the breast without osseous metastases. Detailed case reports are given, including the roentgen technic employed.—E. H. Q.

Roentgenologic Demonstration of Spinal Metastases from Leiomyosarcoma of the Uterus. Robbins, L. L. [Massachusetts General Hosp., Boston, Mass.] *Arch. Surg.*, **47**:463-467. 1943.

A report of 2 cases showing osteoblastic metastases.—W. A. B.

The Effect of Preoperative Irradiation on Adenocarcinoma of the Uterus. Schmitz, H. E., Sheehan, J. F., and Towne, J. [Mercy Hosp. Inst. of Radiation Therapy, and Loyola Univ. Sch. of Med., Chicago, Ill.] *Am. J. Obst. & Gynec.*, **45**:377-390. 1943.

The technic of the authors in treating carcinoma of the uterine fundus with x-ray and radium therapy is described. The authors feel that preoperative irradiation is of definite value, but this treatment is not advocated as a substitute for surgery in patients who are good surgical risks. The authors are continuing to use preoperative irradiation in order to determine whether the number of subsequent 5 year cures is greater than in cases treated by surgery and postoperative irradiation.—A. K.

Treatment of Carcinoma of the Cervix at Charity Hospital. Preliminary Report of End Results. Garcia, M., and Menville, L. J. [Charity Hosp. of Louisiana, and Tulane Univ. of Louisiana Sch. of Med., New Orleans, La.) *New Orleans M. & S. J.*, **96**:87-92. 1943.

An analysis of results of x-ray and radium therapy applied to 226 women with carcinoma of the cervix is presented. These patients were treated between April 1938 and August 1939; 85% were receiving treatment for the first time. Half the treated patients died within 24 months, while half the untreated patients as reported in another series were dead by the end of 9 months. The absolute 3 year survival rate was 37.7%. This compares favorably with the survival rate reported from other clinics where radium therapy was combined with hysterectomy.—E. E. S.

Tissue Dosage in the Control of Carcinoma of the Cervix. Garcia, M. (Charity Hosp., New Orleans, La.) *Radiology*, **40**:463-470. 1943.

In an analysis of 181 cases of cervix carcinoma treated at Charity Hospital, Garcia correlates dosage and treatment time after correction for quality. Longer periods of treatment time require larger doses. From a study of 44 Stage I and II 3 year survivals he concludes that the doses tolerated in the paracervical region are far in excess of the quantity of radiation required for maximum results. It is therefore doubtful whether results in Stage I and II can be improved, but a better definition of the minimum effective dose may make it possible to reduce the dosage given in some cases.—R. E. S.

Further Study of Supervoltage X-Ray Therapy in Carcinoma of the Cervix. Schmitz, H. E. [Loyola Univ. Sch. of Med. and Mercy Hosp., Chicago, Ill.] *Radiology*, **40**:458-462. 1943.

This is a follow-up study of previously reported patients with carcinoma of the cervix treated with radium and 800 kv. roentgen rays. Among 72 cases the 5 year survival was 37.5%. Among patients in clinical groups I and II there was 75% survival, while only 26% of patients in groups III and IV were salvaged.—R. E. S.

Dosage Calculation for Various Combinations of Parametrial Needles and Intracervical Tandems. Nolan, J. F., and Quimby, E. H. [Memorial Hosp., New York, N. Y.] *Radiology*, **40**:391-402. 1943.

Fields of radiation with various combinations of intracervical tandems and interstitial needles were calculated. Various combinations of position, angulation, and mgm./hr. exposures for the interstitial radiation were made. Comparison of the methods is made in tables and graphs.—R. E. S.

Mistakes and Misunderstanding in the Roentgenologic Diagnosis of Gastric Cancer. Kirklin, B. R. [Mayo Clinic, Rochester, Minn.] *Arch. Surg.*, **46**:861-864. 1943.

A general discussion.—W. A. B.

Roentgen Therapy for Bronchiogenic Cancer. WIDMANN, B. P. [Philadelphia General Hosp., Philadelphia, Pa.] *Am. J. Roentgenol.*, **51**:61-69. 1944.

Survival times in 167 cases of bronchiogenic cancer treated with x-rays are compared with corresponding data for 119 untreated cases. It appears that irradiation may prolong life 1 to 6 years in approximately 10% of the cases. In bronchiogenic cancer the disease is often in an advanced stage when the diagnosis is made, and little beyond temporary palliation can be hoped for. However, because of the good results in the exceptional cases, it is urged that all except the few operable ones should be treated intensively by irradiation.—E. H. Q.

Roentgen Irradiation in Polycythemia Vera by Multiple Small Doses to Large Areas of the Body. ROBBINS, L. L. [Massachusetts General Hosp., Boston, Mass.] *Am. J. Roentgenol.*, **51**:230-235. 1944.

A study of 20 cases of polycythemia vera, treated at the Massachusetts General Hospital during the past 10 years, by series of small daily doses of x-rays to large areas of the body, indicates that the method results in longer remissions than have followed other forms of therapy. There are no ill effects from the treatments, which, however, necessitate close following of the white blood count to be sure that the irradiation is stopped at the proper time.—E. H. Q.

Skin and Subcutaneous Tissues

Hochgradige atypische (krebsähnliche) Epithelwucherung in der Haut nach Schutzpockenimpfung. [Highly Atypical Epithelial Growth Resembling Cancer of the Skin After Vaccination.] WALTHARD, B. [Universität Bern, Bern, Switzerland] *Schweiz. med. Wchnschr.*, **72**:1078-1079. 1942.

The pustule was of 20 days' standing, in a 44 year old soldier who suffered a cardiac death while bathing.

Though the hyperplasia was extreme the characteristic atypical cells and nuclei of malignancy were wholly lacking.—W. H. W.

Advanced Cancer of the Face. DECHOLNOKY, T. [Post-Graduate Hosp., New York, N. Y.] *Am. J. Surg.*, **64**: 263-267. 1944.

A case report demonstrating the effectiveness of a radical operation followed by plastic reconstruction.—W. A. B.

Nervous System

Incidence of Metastases to the Nervous System. NEUSTAEDTER, M. [New York Cancer Inst., Welfare Island, N. Y.] *Arch. Neurol. & Psychiat.*, **51**:423-425. 1944.

The incidence of metastatic carcinoma of the nervous system among 6,761 cases examined at the New York Cancer Institute during the 8 year period between 1935 and 1942 was 143 or 2.15%. In metastasis involving the brain, the site of the primary lesion was breast in 14 cases; lung 8 cases; pharynx and larynx, 8; tongue, 4; uterus, 3; rectum, 2; skin, 2; and carcinoma of the bladder, the hard palate and the antrum, 1 each. The order of frequency with which metastases involved the spinal cord was practically the same as the brain involvement. Only 10 cases of sarcoma metastasizing to the nervous system were encountered. The age incidence for males was slightly higher than for females. For males, the peak of incidence fell in the sixth decade, for females in the fifth.—M. E. H.

Racial and Sexual Incidence of Primary Intracranial Tumors. Statistical Study of One Hundred and Thirty-Three Cases Verified by Autopsy. NEWBILL, H. P., and ANDERSON, G. C. [Univ. of Virginia Sch. of Med., Charlottesville, Va., and Louisiana State Univ. Sch. of Med. and Charity Hosp., New Orleans, La.] *Arch. Neurol. & Psychiat.*, **51**:564-567. 1944.

A study based on records of 10,112 autopsies (1929 to 1942 inclusive) performed on patients between the ages of 1 month and 70 years, the age range of intracranial tumors in this series. One hundred and thirty-three primary intracranial tumors were observed. The tumors that did not arise from either glial or meningeal elements showed no sex or race predilection. The frequency of gliomas in white persons was approximately twice that in negroes, and was most frequent in white females. Meningioma was approximately three times as frequent in white persons as in negroes. Of the 28 meningiomas present, 12 occurred in white females.—M. E. H.

Primary Sarcomas of the Brain. Review of the Literature and Report of Twelve Cases. ABBOTT, K. H., and KERNOHAN, J. W. [Mayo Clinic, Rochester, Minn.] *Arch. Neurol & Psychiat.*, **50**:43-66. 1943.

Twelve cases of tumors classified as "primary sarcoma of the brain" are reported. These lesions, arising in the brain as primary tumors, have been classified as fibrosarcoma (3 cases), perivascular sarcoma (7 cases), and sarcoma of unknown type (2 cases, in both of which the tumor probably belonged to one of the aforementioned two types).—M. E. H.

Reticulum Cell Sarcoma of the Brain. KINNEY, T. D., and ADAMS, R. D. [Boston City Hosp., and Harvard Med. Sch., Boston, Mass.] *Arch. Neurol & Psychiat.*, **50**:552-564. 1943.

Two cases of a primary tumor of the temporal lobe, identical in every respect with reticulum cell sarcoma occurring in other organs of the body, are presented with complete autopsy reports.—M. E. H.

Progressive Multiform Angiosis. Association of a Cerebral Angioma, Aneurysms and Other Vascular Changes in the Brain. ARIETI, S., and GRAY, E. W. [Pilgrim State Hosp., Brentwood, N. Y.] *Arch. Neurol. & Psychiat.*, **51**:182-189. 1944.

Case report. No sharp distinction is possible between vascular malformations and vascular tumors of the brain. All the vascular lesions present in this case probably belong to one pathologic entity. Hence the term "progressive multiform angiosis" is proposed.—M. E. H.

Erroneous Diagnosis of Brain Tumor; Report of 17 Cases. MARSHALL, M. Y. [Veterans Admin., Wadsworth, Kans.] *M. Bull. Vet. Admin.*, **20**:253-273. 1944.

The author reviews the clinical histories, physical examinations, and autopsy findings in 17 cases of brain tumor in which the original diagnosis was incorrect. In analyzing the diagnostic failures he found that part of the fault seemed to rest on the absence of "brain tumor consciousness" on the part of the examiner. X-rays of the

skull, estimation of the total protein content of the spinal fluid, and encephalography should be made routine parts of the examination. Surgery of the brain is improving, and a pessimistic attitude toward surgical treatment is no longer justified.—M. E. H.

The Human Pyramidal Tract. IX. Effect of paralysis Produced by Cerebral Tumors on Axons of the Pyramids. LASSEK, A. M. [Med. Coll. of State of South Carolina, Charleston, S. C., and Coll. of Physicians & Surgeons, Columbia Univ., New York, N. Y.] *Arch. Neurol. & Psychiat.,* **51**:213-215. 1944.

In cases of cerebral tumor, unilateral motor deficit with one or more pyramidal tract signs may occur with little or no loss of axons in the pyramidal tract. Destruction was complete in 8 or 6.7% of the 119 cases reviewed, and the tumors here were widespread. Apparently tumors located in any part of the cerebrum may produce motor difficulties with signs of damage to the pyramidal tract.—M. E. H.

Diffuse Hypertrophy of the Cerebellar Cortex (Myelinated Neurocytoma) Report of a Case. DUNCAN, D., and SNODGRASS, S. R. [Univ. of Texas, Galveston, Tex., and Univ. of Buffalo, Buffalo, N. Y.] *Arch. Neurol. & Psychiat.,* **50**:677-684. 1943.

A case of diffuse hypertrophy of the left cerebellar cortex leading to signs and symptoms of a cerebellar neoplasm is described. Histologically, the growth was composed of adult neurons arranged in nearly normal pattern, but with the individual elements greatly enlarged. Most of the enlarged cells appeared to be derived from the granule and the stellate cells of the cerebellum.—M. E. H.

Tumor of the Acoustic Nerve Within the Petrous Bone. Operative Removal. ADELSTEIN, L. J., and ANDERSON, F. M. [Los Angeles County General Hosp., and Univ. of Southern California Sch. of Med., Los Angeles, Calif.] *Arch. Neurol. & Psychiat.,* **51**:268-270. 1944.

Case report. The tumor produced definite cerebellar signs, together with slight impairment of function of the trigeminal nerve, diminution of the deep reflexes on the opposite side of the body, and increase in intracranial pressure. Tumors of such a size confined entirely to the intrapetrous portion of the acoustic nerve are uncommon.—M. E. H.

EYE

Cancer of the Eyelid. HOLLANDER, L., and KRUGH, F. J. [Pittsburgh Skin and Cancer Foundation, Pittsburgh, Pa., and East Point, Ga.] *Am. J. Ophth.,* **27**:244-253. 1944.

The authors state that 9% of all skin cancers occur in the eyelids though rarely at the mucocutaneous seam. The majority of eyelid cancers were found to be of the basal-cell or hair-matrix-cell variety.—E. C. R.

Glioma of the Optic Nerve. REULING, F. H. [Waterloo, Iowa] *J. Iowa State Med. Soc.,* **33**:422-424. 1943.

Report of a case in a 10 year old boy. The tumor was removed, and recovery uneventful.—A. C.

A Rare Retinal Tumor Probably Derived from Müller's Fibers. ORTON, R. H., and WILLIS, R. A. [Pathological Dept. of the Victorian Eye and Ear Hosp., and the Alfred Hosp., Melbourne, Australia] *J. Path. & Bact.,* **56**:255-257. 1944.

The article deals with the histology of a hitherto undescribed tumor, which almost filled the vitreal cavity and which arose in the retina and not in the ciliary body. The tumor is composed of elongated cells with narrow processes attached at either end, which correspond to the vertical sustentacular cells or fibres of Müller.

On histological grounds the authors excluded retinoblastoma, pigmented epithelial tumor of the retina, astrocytic gliomas (arising from the sustentacular spider cells of the retina), astrocytic gliosis, ganglion neuroma, or any connective tissue tumor.—L. W. P.

BREAST

Tumour of the Breast Treated with Stilboestrol. BROWN, T. D., CORRESPONDENCE. Brit. M. J., **1**:731. 1944.

A description of a result apparently favorable in a patient aged 90.—E. L. K.

Lesions of the Breast. The Relationship of Benign Lesions to Carcinoma. CLAGETT, O. T., PLIMPTON, N. C., and ROOT, G. T. [Mayo Clinic, Rochester, Minn.] *Surgery,* **15**:413-419. 1944.

The incidence of carcinoma of the breast among 382 patients, who had had excision of a benign breast lesion (fibroadenoma, chronic cystic mastitis) 5 to 6 years previously, was 1.8%. This is 5 times greater than the incidence of carcinoma of the breast in the population of women from 25 to 65 years of age in Minnesota for 1940. Carcinoma did not occur in any case of fibroadenoma or "comedomastitis," but was present in 3.3% of patients with chronic cystic mastitis, and in 1.6% of those with chronic mastitis.—W. A. B.

Chronic Cystic Mastitis. COLE, W. H., and ROSSITER, L. J. [Chicago, Ill.] *Proc. Inst. Med. Chicago,* **15**:92-93. 1944.

The authors divide the disease into four groups, (1) adenofibrosis, (2) benign parenchymatous hyperplasia, (3) precancerous hyperplasia and (4) cystic disease. Adenofibrosis and cystic disease rarely undergo transformation to carcinoma. Benign parenchymatous and precancerous hyperplasia may undergo malignant transformation if they are present long enough. The classification has been made with the idea of offering aid regarding therapy.—M. E. H.

Carcinoma of the Breast. II. Criteria of Operability. HAAGENSEN, C. D., and STOUT, A. P. [Presbyterian Hosp., and Columbia Univ., New York, N. Y.] *Ann. Surg.,* **118**:859-870, 1032-1051. 1943.

On the basis of a study of 640 cases of carcinoma of the breast with radical mastectomy, rules were formulated for determining when to perform this operation. The number of cures would not have been altered had the criteria been used and operation avoided in 109 of the cases. Cases considered categorically inoperable are those with extensive edema of the breast, satellite, or intercostal, or parasternal nodules in the skin, preoperative edema of the arm, proven supraclavicular metastases, inflammatory carcinoma, distant metastases, or carcinoma appearing during pregnancy or lactation. There were no permanent cures in 74 cases having one of these findings. Operation is also contraindicated when 2 or more of the following signs are present: skin ulceration, edema of less than

one-third of the skin of the breast, fixation of the neoplasm to the chest wall, axillary nodes 2.5 cm. or more in diameter containing metastases, and fixation of axillary nodes with metastatic tumor to the skin. These and other data indicate that radical mastectomy in far advanced local disease shortens life expectancy.—W. J. B.

Swelling of the Upper Extremity Following Radical Mastectomy. Holman, C., McSwain, B., and Beal, J. M. [New York Hosp. and Cornell Univ. Med. Coll., New York, N. Y.] *Surgery* **15**:757-765. 1944.

One hundred patients subjected to 103 radical mastectomies were studied. The occurrence of postoperative swelling of the arm did not necessarily mean recurrence of carcinoma. The presence or absence of axillary metastases bore no relationship to the swelling nor did the use of primary skin grafts. The most significant factors in the cause of swelling were infection and x-ray dermatitis.—W. A. B.

Bilateral Oophorectomy with Radical Operation for Cancer of the Breast. Horsley, J. S. [St. Elizabeth's Hosp., Richmond, Va.] *Surgery* **15**:590-601. 1944.

The author performs bilateral oophorectomy in combination with radical mastectomy in premenopausal women in order to (a) eliminate the effect of estrogenic substances and (b) prevent pregnancy with its deleterious effects.—W. A. B.

Value of Surgery and X-Ray Treatments in Carcinoma of the Breast. Pettit, R. T. [Ottawa, Ill.] *Illinois M. J.*, **85**:244-247. 1944.

A statistical report of 193 cases treated between 1928 and 1937. The conclusions are drawn that x-ray therapy properly administered and in adequate dosage is a valuable adjunct to surgery and that combined x-ray and surgical treatment offers the patient the best chance for permanent cure.—M. E. H.

Female Genital Tract

Two Cases of Brenner Tumor: One of Unusual Size. Reel, P. J., and Foster, P. C. [Columbus, Ohio; and Gallipolis, Ohio] *Ohio State M. J.*, **39**:919-921. 1943.

The reason for presenting one of these patients is mentioned in the title. The tumor, measuring 28 cm. in its greatest diameter, was removed from a 64 year old colored woman and proved to be of the solid type. By contrast the other tumor, also of the solid variety, measured 1.5 cm. across and occurred in a young woman. It had no unusual features.—E. E. S.

Androgen Therapy in Pelvic Malignancy. Beecham, C. T. [Temple Univ. Med. Sch., Philadelphia, Pa.] *Am. J. Obst. & Gynec.*, **46**:849-852. 1943.

Four patients with ovarian carcinoma and 2 with carcinoma of the cervix, all judged clinically to be in a hopeless condition, were treated with testosterone propionate. Hormone therapy did not inhibit the extension of the growth. In one patient with an ovarian tumor and metastases in bladder, peritoneum, and bowel walls, who was treated by surgery and x-ray, administration of testosterone propionate failed to relieve pain and was followed by distressing effects. In the remaining 5 patients, there was relief of pain and temporary improvement in general condition.—A. K.

The Accepted Treatment for Malignancy of the Uterus. A Therapeutic Anachronism. Kennedy, J. W. [Philadelphia, Pa.] *M. Rec.*, **156**:546-548, 554. 1943.

The author pleads for vaginal hysterectomy by the clamp method for carcinoma of fundus or cervix and sees no benefit and considerable harm in a preliminary biopsy or curettage. No details of results of the recommended method are given. Since a cautery is used on the cervix before hysterectomy, there is no way of confirming the author's diagnosis, and his conviction that cancer was present in the organ removed is based purely on personal clinical observation. The use of radium or x-ray is dismissed as useless, without comparison of results.—E. E. S.

The Surgical Treatment of Cancer of the Body of the Uterus in the Obese. Frank, L. W. [Louisville, Ky.] *South. M. J.*, **37**:24-26. 1944.

In order to avoid contamination that occurs when pads of extraperitoneal fat of the abdominal wall roll over the vagina when it is cut away in the usual total hystrectomy, in obese patients the author performs a subtotal hysterectomy plus bilateral salpingo-oophorectomy and thoroughly cauterizes the mucosa of the remaining cervical stump from above. A two-fold purpose is served: first, the cervical mucosa which may be the focus for "recurrent" cancer is destroyed; second, contamination from the cervical stump is "eliminated." This procedure was done on 7 obese patients observed from 1½ to more than 5 years and there have been no recurrences.—W. A. B.

Cancer of the Uterus: The Vaginal Smear in Its Diagnosis. Traut, H. F., and Papanicolaou, G. N. [Univ. of California Med. Sch., San Francisco, Calif., and Cornell Med. Coll., New York, N. Y.] *California & West. Med.*, **59**:120-122. 1943.

By the examination of stained vaginal smears the presence of cancer of the cervix was shown in all but 1.3% of the cases in which it was demonstrated by biopsy. In 13 instances, adenocarcinoma was revealed for the first time by the vaginal smear when no other clinical procedure had sufficed to make the diagnosis.—W. A. B.

The Early Diagnosis of Cancer of the Cervix. Campbell, R. E. [Univ. of Wisconsin Med. Sch., Madison, Wis.] *Wisconsin M. J.*, **43**:301-305. 1944.

Public education to develop cancer consciousness, periodic and complete physical examinations combined with biopsies of suspicious lesions are essential to the early diagnosis of carcinoma of the cervix.—M. E. H.

Factors in the Management of Cancer of the Uterine Cervix. Campbell, J. A. [Indiana Univ. Sch. of Med. and hospitals, Indianapolis, Ind.] *J. Indiana M. A.*, **36**:181-186. 1943.

A general discussion. The treatment of choice is said to be radiation therapy, but the initial treatment must be an intensive one. The details of application are given; best results are said to be obtained by a combination of x-ray and radium.—E. E. S.

Carcinoma of the Cervix—The Wertheim Operation. Meigs, J. V. [Pondville Hosp., and the Vincent Memorial Hosp., Boston, Mass.] *Surg. Gynec. & Obst.*, **78**:195-199. 1944.

The author has employed radical excision—the Wertheim operation, plus the Taussig method of dissecting the

pelvic lymph nodes—in 53 patients with carcinoma of the cervix. The operative mortality was nil in 47 elective cases, but complications due to ureteral injury were frequent (10% or more). Twenty-two of his patients are alive more than 1 year after the operation, 9 have survived more than 2 years, and 5 have remained alive 3 to 4 years. Only 3 have died—1 after 2 years and 2 months, and 2 in less than a year following the operation. The author believes that this method of treatment of cervical cancer will give better end results than present methods of radiation.—J. G. K.

Carcinoma of the Cervix. MEIGS, J. V. [Harvard Med. Sch., and Massachusetts General Hosp., Boston, Mass.] *New England J. Med.*, **230**:577-582. 1944.

A review article in the Medical Progress Annual series. Discussion of etiology, symptomatology, diagnosis, classification, and treatment. To be concluded.—C. W.

MALE GENITAL TRACT

The Incidence of Coincident Prostatic Calculi, Prostatic Hyperplasia and Carcinoma of the Prostate Gland. CRISTOL, D. S., and EMMETT, J. L. [Mayo Clinic, Rochester, Minn.] *J. A. M. A.*, **124**:646. 1944.

A study of a large series of records suggests that the incidence of prostatic calculi in cases of hyperplasia and in cases of carcinoma of the prostate is practically identical.—M. E. H.

Treatment of Prostatic Carcinoma. BARRINGER, B. S. [Memorial Hosp., New York, N. Y.] *Bull. N. Y. Acad. of Med.*, **19**:417-422. 1943.

It is stated that the presence of a carcinoma in the early stages can be established in about 70% of the patients by aspiration biopsy. The serum acid phosphatase is usually elevated if the tumor is invading the blood stream, and the alkaline phosphatase should be high if osteoblastic metastases are present in the skeleton. Simple orchidectomy causes complete regression of the tumor and of bone metastases in very few patients; the additional treatment of the administration of the antiandrogen, stilbestrol, is advised. The drug alone causes regression of the primary tumor but does not affect the growths in bone.—E. E. S.

Carcinoma of the Prostate: Recent Advances in Its Treatment. BERGMAN, R. T. [Coll. of Medical Evangelists, Los Angeles, Calif.] *California & West. Med.*, **58**:71-73. 1943.

General discussion and report of the treatment during the past year of 31 cases, by means of castration, estradiol dipropionate, stilbestrol, or a combination of these. There was relief of pain in all but 3 patients. Clinical improvement was noted in some instances.—W. A. B.

The Effect of Orchidectomy and Stilbestrol in Carcinoma of the Prostate. HERGER, C. C., and SAUER, H. R. [State Inst. for Study of Malignant Diseases, Buffalo, N. Y.] *Am. J. Surg.*, **62**:185-200. 1943.

The study is based on 82 patients among whom positive biopsy was obtained in 70 (85.4%). Metastases were evident in 30 (36.6%). Stilbestrol alone was administered to 60 patients, orchidectomy alone was carried out in 3, and in 19 castration was preceded or followed by stilbestrol therapy. Thirteen (21.7%) of those who received stilbestrol alone were improved (gain in appetite, weight, and sense of well-being) as compared with the 3 patients subjected to orchidectomy and 10 who had combined therapy (59%). Similar improvement obtained in patients with metastases. Of interest was the complete disappearance of metastatic lymph nodes in each of 3 patients; 2 of the 3 had received stilbestrol alone, the third had been castrated also. Improvement in the x-ray appearance of metastatic bone lesions was found in but 3 of 27 patients.

There was a consistent elevation of serum acid phosphatase activity (above 4.0 King-Armstrong units) in 27 patients. Orchidectomy alone (2 patients) or combined with stilbestrol (15 patients) was done in 17 patients with elevated serum acid phosphatase activity (average 150.7 units), resulting in a mean decline of 59.6% of the preoperative level on the second postoperative day, 75.4% one week after orchidectomy, and 92.2% after 3 weeks. Among 10 patients with elevated values for serum acid phosphatase treated with stilbestrol alone, a decrease of serum acid phosphatase activity occurred in but 5, declining 56.8% of the original values in 2 days, 63.8% after 1 week, and 90.6% after 3 weeks.

Following orchidectomy in 13 patients studied, there was a transient increase in the alkaline phosphatase during the third week to about twice the preoperative value. There was no significant change in the serum alkaline phosphatase activity in patients treated with stilbestrol alone.

Among patients with differentiated carcinoma, improvement occurred in 31%, while 53% with undifferentiated carcinoma were benefited by treatment.

The authors believe that castration should be done in all patients with cancer of the prostate with metastases and in those who do not respond favorably to stilbestrol therapy. While stilbestrol may accelerate improvement in patients who respond favorably to castration, it is ineffective in patients who fail to respond.—W. A. B.

Clinical and Pathologic Effects of Diethylstilbesterol and Diethylstilbesterol Dipropionate on Carcinoma of the Prostate Gland. A Continuing Study. KAHLE, P. J., SCHENKEN, J. R., and BURNS, E. L. [Louisiana State Univ. and Charity Hosp. of Louisiana, New Orleans, La.] *J. Urol.*, **50**:711-732. 1943.

The authors have followed 5 patients with prostatic carcinoma since March 1940. Treatment consisted of the administration of diethylstilbesterol and diethylstilbesterol dipropionate. All patients have definite regression in carcinomatous tissue, but 1 died of urinary sepsis and cardiac failure. The remaining 4 continued their initial improvement. From histologic examinations of removed tissue, the authors believe they can point out stages of regressive changes. At first there is a decrease in size of the nuclei, nucleoli become invisible, and mitoses disappear. Cytoplasmic vacuoles form, increase, and rupture the cell membranes. The nuclei become pyknotic. Finally only stroma remains. There are 19 text figures.—V. F. M.

Orchiectomy in the Treatment of Cancer of the Prostate Gland. KRETSCHMER, H. L. [Presbyterian Hosp., Chicago, Ill.] *J. A. M. A.*, **123**:755-757. 1943.

A review of 11 cases in which this therapeutic procedure was carried out. The author feels the results are anything but desirable and urges an evaluation of the efficacy of castration in this form of cancer.—M. E. H.

The Modern Treatment of Prostatic Cancer—A Rational Basis for Delayed Hormone Therapy. NESBIT, R. M., and CUMMINGS, R. H. [Univ. of Michigan, Ann Arbor, Mich.] *J. Indiana M. A.*, **36**:577-579. 1943.

This is a follow-up report on 75 patients with infiltrating prostatic cancer treated by orchidectomy. With few exceptions pain was greatly relieved and more than half the patients gained weight. Those complaining of difficulty in voiding experienced more normal urination subsequent to castration. Even the symptoms of transverse myelitis were diminished but later returned; patients with these symptoms died. In summary, the authors state that 65 of the 75 patients were improved clinically, but in many the benefit was transient. They therefore conclude that maximum benefit to the patient may be obtained by delaying orchidectomy until advanced stages of the disease are reached, thus assuring the longest period of palliative relief.—E. E. S.

Prostatic Carcinoma Treated by Orchiectomy. A Second Report Based on Seventy-five Cases Observed for at Least Twenty-One Months Following Operation. NESBIT, R. M., and CUMMINGS, R. H. [Univ. of Michigan Med. Sch., Ann Arbor, Mich.] *J. A. M. A.*, **124**: 80-81.] 1944.

This second follow-up study of 75 patients gives continued evidence of the value of this form of treatment. Thirty-four patients (45%) remain free from symptoms 21 to 36 months after orchidectomy. Twenty-one (28%) have shown recurrent symptoms since the last report and several have died. The increasing incidence of delayed failure in this series suggests that all cases may fall into this category eventually. The suggestion is made that the maximum benefit to the patient may be obtained if endocrine therapy is delayed until indicated by the onset of symptoms arising from advanced or metastatic lesions.—M. E. H.

Carcinoma of the Prostate. PRINCE, C. L., and VEST, S. A. [Univ. of Virginia Hosp., Charlottesville, Va.] *South M. J.*, **36**:680-685. 1943.

A review of 189 cases. Length of life varied following different palliative measures: no treatment (11 patients), av. 21 months; deep x-ray alone (10 patients), 16 months; suprapubic prostatectomy (5 patients), 25 months; transurethral resection (40 patients), 27.3 months; and transurethral resection plus radon (7 patients), 36 months. Of 77 cases of carcinoma of the prostate seen in the past 3 years, 7 (9%) were considered suitable for radical perineal prostatectomy, which was done with 1 death. This operation is recommended as the only possible cure of carcinoma of the prostate.—W. A. B.

Cancer of the Prostate. WRIGHT, B. W. [Nashville, Tenn.] *J. Tennessee M. A.*, **36**:223-225. 1943.

About 70% of these carcinomas arise in the posterior part of the gland, where hyperplasia does not occur, and spread to the seminal vesicles. Therefore radical removal of the gland is necessary for cure. There is a brief statement concerning the retardation of growth of prostatic carcinoma and diminution in discomfort following orchidectomy, radiation of the testes, or administration of estrogenic substances, but it is clear that such measures are only palliative, and cure can be effected by surgical methods alone.—E. E. S.

Carcinoma of the Prostate Treated with Stilboestrol. FERGUSSON, J. D. [Central Middlesex County Hosp., London, England] *Lancet*, **1**:595-597. 1944.

The author records his experience during the last 15 months, but emphasizes that the duration of life in cases of carcinoma of the prostate may be much longer than is usually supposed, and that no cure could be considered to be proved in less than 5 years. The methods of diagnosis are described and discussed; serum acid phosphatase greater than 2.5 King-Armstrong units is confirmatory, but a low or normal value does not exclude malignancy. The usual initial dose was 5 mgm. by mouth twice or thrice daily; later a maintenance dose of 1 to 2 mgm. twice daily may suffice. The response may be rapid; in a favorable case frequency diminishes, micturition is easier, and the prostate may become smaller and softer. In cases with retention and infection the residual urine is reduced and may become clear and sterile. The patient may be able to lead a much more active life. The relief of edema in advanced cases is striking. "I am acquainted with one case in which metastatic subcutaneous nodules have disappeared." Discontinuance of the dose is likely to be followed by return of symptoms. There may be tenderness and enlargement of the breasts, dizziness, headache, and irritation of the skin. "There is some evidence to suggest that cerebral hemorrhage is commoner in patients receiving stilbestrol than one would expect at this age." In the last 15 months the author has treated 18 patients, of whom 6 were admitted moribund and died within a month; of 8 survivors (average age 70) 2 show little improvement but no deterioration, and 6 are much improved and virtually symptom-free.—E. L. K.

Two Cases of Interstitial-Cell Tumour of the Human Testis. BONSER, G. M., and HAWKSLEY, L. M. [Univ. of Leeds, and Royal Cancer Hosp. (Free), London, England] *J. Path. & Bact.*, **55**:295-299. 1943.

Two cases of interstitial-cell tumor of the human testis are described. Both tumors were believed to be of low-grade malignancy, and their growth was unaccompanied by any generalized endocrine disturbance as shown by impotence, gynaecomastia, or other signs. Some comparisons are drawn between this type of tumor as it occurs spontaneously in man and the dog and the similar tumors induced experimentally in the mouse by excess of estrogen. There are 5 figures.—A. H.

Adenocarcinoma of the Testis. WATERMAN, J. L., and BRINES, O. A. *U. S. Nav. M. Bull.*, **41**:1690-1693. 1943.

Case report of a nonembryonal type of tumor and recommendations concerning terminology and classification.—C. W.

Extragenital Chorioma: Its Relation to Teratoid Vestiges in the Testicles. ROTTINO, A., and DEBELLIS, H. [St. Vincent's Hosp., New York, N. Y.] *Arch. Path.*, **37**:78-80. 1944.

Report of a case in a 37 year old white man in which a small cyst lined by stratified squamous epithelium was found in one testicle and widespread chorioma elsewhere.—J. G. K.

Malignancy of the Epididymis. With Report of a Case of Teratoma of the Epididymis. CRABTREE, E. G. [Boston, Mass.] *J. Urol.*, **50**:733-739. 1943.

All types of tumor that occur in the testis could reasonably be expected to appear primarily in the epididymis also. A definite instance of teratoma of the epididymis has not been demonstrated prior to the one reported here. The patient described is free of disease 20 months after orchidectomy. Microscopically, the lesion was complex in structure showing transitional epithelium, epithelium resembling skin, columnar epithelium, cysts, myxomatous tissue, smooth muscle, and other tissues. The mass was in the epididymis, but microscopically neoplastic tissue was found in the tunica albuginea.—V. F. M.

Penile Cancer. Report of a Case in a Luetic; Review of the Literature. Discussion and Treatment. LAUGHLIN, V. C. [Cleveland, Ohio] *Ohio State M. J.*, **39**:35-39. 1943.

A report of the occurrence of a squamous cell carcinoma in a 41 year old male who had had a chancre and had received antiluetic therapy for 2 years as the tumor grew. Treatment included amputation of the penis and deep radiation of pelvic and inguinal lymph nodes. The relationship of this tumor to trauma associated with unhygienic conditions is discussed. There is a brief review of the pathology, symptoms, and prognosis; the latter is excellent if the tumor is treated by radical excision. Clinical differentiation from a variety of lesions is discussed in detail.—E. E. S.

ORAL CAVITY AND UPPER RESPIRATORY TRACT

Oral Cancer in Bombay, India. A Review of 1,000 Consecutive Cases. KHANOLKAR, V. R. [Tata Memorial Hosp., Bombay, India] *Cancer Research*, **4**:313-319. 1944.

One thousand consecutive cases of oral cancer seen at the Tata Memorial Hospital during the past 30 months have been reviewed.

Differences in the distribution of oral cancer according to site between communities in Bombay and between similar data at other hospitals have been pointed out and discussed.—Author's summary.

Treatment of Carcinoma of the Lip with Special Reference to the Management of the Regional Lymph Nodes. WILSON, H. [Univ. of Tennessee, Memphis, Tenn.] *J. Tennessee M. A.*, **36**:140-144. 1943.

Emphasis is placed on the need for complete exploration of the lymph nodes likely to be the seat of metastases from lip carcinoma. Diagnosis of the type of tumor should be first established by biopsy regardless of how obvious it may seem. Surgical extirpation, roentgen rays, or radium may be used to treat the primary tumor according to size and location of the growth. The lymph nodes of the neck and parotid region should be dissected even if small; in most instances radiation is not a suitable procedure. It is best to treat the primary tumor and the metastases at different times.—E. E. S.

Carcinoma of the Tip of the Tongue. A Case of Metastasis from a Malignant Tumor of the Breast. FINK, I., and GARB, J. [Harlem Hosp., New York, N. Y.] *Am. J. Surg.*, **62**:138-141. 1943.

Case report.—W. A. B.

Carcinoma of the Gum. JOHNSON, G. S., and DANIEL, R. A. [Vanderbilt Univ. Sch. of Med., Nashville, Tenn.] *Ann. Surg.*, **117**:74-84. 1943.

Epidermoid carcinoma of the alveolar margin invades the underlying bone, producing pain relatively early in the disease, and the authors have studied cases of this condition in the hope of improving the usual poor results of therapy. In the Vanderbilt University Hospital before 1933 when neoplasms of this type were treated with radium or x-ray therapy, no cures were obtained; the average period of survival is not stated. Since 1933 the procedure of choice has been a suprahyoid neck dissection, removal of soft tissues from the mandible, and cauterization of the mandible with hot soldering irons, under chloroform anesthesia. Sequestration is complete in from 2 to 5 months; closure of the oral fistula and plastic procedures may then be performed. This operation was carried out in 12 of 23 cases of squamous cell carcinoma of the lower gum; 5 patients with tumors that were considered operable refused operation. The average duration of life after onset in the group not operated on was 14 months. In all except 3 of these cases some other form of treatment was given. Among the patients operated upon, 1 died within 12 hours. In 4 patients dying of recurrence, the average period from the beginning of symptoms was 17.7 months. One patient died 3 years after operation without evidence of recurrence. Six patients are living and well 4 or more years postoperatively. In all except 2 of the patients, both of whom are still alive, roentgen therapy to the neck was given.—W. J. B.

Mixed Tumors of the Palate. ROSEDALE, R. S. [Canton, Ohio] *Ohio State M. J.*, **39**:235-237. 1943.

A list is given of the reported cases of this rare tumor. The clinical and histologic features of such a tumor in a 63 year old woman are described. The tumor had been present for more than 20 years but was enlarging prior to resection. There was no recurrence.—E. E. S.

Carcinoma of the Larynx. SCHALL, L. A. [Boston, Mass.] *New England J. Med.*, **229**:574-576. 1943.

A short review paper including a description of the construction and use of an "artificial larynx." The management of various types of cases is described. There is no bibliography.—C. W.

INTRATHORACIC TUMORS—LUNGS—PLEURA

Cervicomediastinal Lymphangioma (Cystic Hygroma). Report of Two Cases in Infants. ARNHEIM, E. E. [Mt. Sinai Hosp., New York, N. Y.] *J. Mt. Sinai Hosp.*, **10**:404-410. 1943.

Approximately 225 cases of cystic hygroma of the neck

have been reported up to the present time. In only 3 instances was there involvement of both the neck and mediastinum. Two successfully treated infants with this condition are recorded by the author. The embryologic, pathologic, and clinical features, and the treatment of cervicomediastinal lymphangioma are reviewed.—A. Cnl.

Resection of the Left Vagus Nerve for Multiple Intrathoracic Neurofibromas. Blades, B., and Dugan, D. J. [Walter Reed General Hosp., Washington, D. C.] *J. A. M. A.*, **123**: 409-410. 1943.

A case report. In order to remove the tumors involving the vagus, it was necessary to resect 15 cm. of the nerve itself. No deleterious effects were noted following the nerve resection.—M. E. H.

Carcinoma of the Lung: The Value of Sputum Examination in Diagnosis. Gowar, F. J. S. [The London Hosp., London, England] *Brit. J. Surg.*, **30**:193-200. 1943.

The sputum from 93 patients in whom neoplasm of the lung was suspected was examined by the wet-film method; cells regarded as malignant were found in 64% of cases of "proved or probable carcinomata," and of these a significant proportion were operable.—E. L. K.

Primary Bronchogenic Carcinoma. Report of a Case. Hetzel, C. C., Jr., and Walker, J. H. [McChord Field, Wash.] *Am. J. Surg.*, **62**:419-421. 1943.

Case report.—W. A. B.

Latent Bronchogenic Carcinoma. Karsner, H. T. [Cleveland, Ohio] *Ohio State M. J.*, **39**:245-246. 1943.

Presentation of the clinical and pathologic features of a case of small cell bronchogenic tumor whose metastases to bones of the skull provided the initial symptoms. It is noted that the presence of a tumor in the lung is often unrecognized until well after metastases have been demonstrated.—E. E. S.

The Morphology of Primary Carcinoma of the Human Lung. Summary and Discussion of the Pathologic Anatomy in 45 Cases. Mulligan, R. M., and Harper, F. R., [Univ. of Colorado, Sch. of Med. and Hosps., Denver, Colo.] *J. Thor. Surg.*, **12**:734-752. 1943.

All but one of the 45 tumors indicated in the title were studied at autopsy; the observations recorded are based also on 50 lung carcinomas from the Chest Tumor Registry. The gross and the histologic character of the various types of lung cancer are described in detail with numerous photographic illustrations. Their mode of extension and metastasis and the secondary changes evoked in the lungs and pleurae are described. Changes in other organs were not found to be striking, but the average thickness of the right ventricular wall was increased without evidence of congestive failure.—E. E. S.

Bronchiogenic Carcinoma: The Role of Bronchoscopy. Samson, P. C. [Alameda Co. Hosp., Oakland, Calif.] *California & West. Med.*, **58**:109-110. 1943.

General discussion.—W. A. B.

Incidence of Primary Carcinoma of the Lung with Special Reference to its Increase. Steiner, P. E. [Univ. of Chicago, Chicago, Ill.] *Arch. Path.*, **37**:185-195. 1944.

Discussion, based on 126 cases from a total of 5,515 necropsies performed during the 40 years from 1902 to 1941. The author believes that there has been a slight apparent increase but no real increase in the incidence of primary carcinoma to the lung.—J. G. K.

Pulmonary Mucous Epithelial Hyperplasia (Pulmonary Adenomatosis). A Report of Two Cases. Taft, E. B., and Nickerson, D. A. [Boston City Hosp., Boston, Mass., Salem Hosp., Salem, Mass., and the Boston Univ. Sch. of Med., Boston, Mass.] *Am. J. Path.*, **20**:395-411. 1944.

The cases were essentially similar to those previously reported, though complicated by severe superimposed bacterial infections.—J. G. K.

Solitary Circumscribed Tumors of the Lung. Thornton, T. F., Jr., Adams, W. E., and Bloch, R. G. [Univ. of Chicago, Chicago, Ill.] *Surg., Gynec. & Obst.*, **78**:364-370. 1944.

A clinical discussion based on a study of 23 patients.—J. G. K.

Gastrointestinal Tract

Carcinoma of the Esophagus in Association with Achalasia of the Cardia. Bersack, S. R. [Veterans Adm. Facility, Hines, Ill.] *Radiology*, **42**:220-223. 1944.

Of a series of 227 cases of achalasia only 1 patient had carcinoma of the esophagus. In spite of the strong exciting factors of irritation by food and stagnation, no definite correlation between carcinoma and achalasia has been established.—R. E. S.

Discussion on the Treatment of Carcinoma of the Œsophagus. The Royal Society of Medicine, London, England. Section of Laryngology. *Proc. Roy. Soc. Med.*, **37**:331-340. 1944.

Mr. Hermon Taylor stated that a less pessimistic and more vigorous attitude towards carcinoma of the esophagus was now indicated. He condemned gastrostomy as a palliative measure since the fistula was distressing and saliva still had to be expectorated and recommended Souttar's tubes or endoscopic insertion of radon seeds as the best means of palliation. He advocated surgery for attempted cure and recommended resection of the affected part of the esophagus with immediate subcutaneous anastomosis outside the thorax, the stomach being drawn up beneath the skin in front of the sternum. Leakage of the anastomosis was not fatal, and if it did occur could be bridged by a short indwelling tube.

Dr. W. M. Levitt stated that radiotherapy could achieve remarkable palliation but was not curative. The most important contraindication to radiotherapy was mediastinitis which had two cardinal signs—substernal pain and persistent tachycardia usually without pyrexia. He regarded lower-third tumors as untreatable by radiotherapy.

Dr. G. H. Steele advocated radon seed implant through the esophagoscope as giving great relief with a minimum of upset. He thought that the only justification for surgery was the poor results obtained by other means and stated that esophagectomy was at the stage gastrectomy was 30 to 40 years ago; it had been shown to be feasible, but the indications for its employment were not yet fully established.

Dr. M. Lederman advocated teleradium for tumors of the cervical esophagus, provided that they had not ex-

tended below the level of the first dorsal vertebra. He recommended the use of a radium bougie for tumors of the thoracic esophagus, using three 25 mgm. tubes on alternate days for a total of 60 hours over a 15 day period. He said that a shift method should be employed, the radium being lowered by half the length of one radium container for alternate treatments to produce a better distribution of the energy absorbed. Tumors of the lower limit of the esophagus could be treated by the insertion of radon seeds after laparotomy.

Other speakers advocated x-ray treatment (4 patients alive and well for over 5 years were referred to), implantation of radon seeds, and surgery (resection and anastomosis in the chest).—W. V. M.

Carcinoma of the Stomach: Early Recognition and Results. PRIESTLY, J. T. [Rochester, Minn.] *J. Iowa M. Soc.*, **33**:1-5. 1943.

Surgical treatment offers the only present hope of cure in gastric carcinoma. Early recognition of the disease is essential if the percentage of cures is to be increased. Early cancer of the stomach may give rise to the so-called "typical," "ulcer," or "nondescript" history. The characteristics of each are given by the author. Competent roentgenologic examination should be insisted upon whenever there is the slightest suspicion of gastric carcinoma. Late diagnosis results from a variety of factors, some of which are inherent in the lesion, some of which the patient is responsible for, and others of which are the responsibility of the medical profession. Of patients who have gastric resection performed for carcinoma, one may expect 29% to be living 5 years later, 20% 10 years later, and 12% 15 years later.—J. L. M.

Benign Gastric Tumor. (The Finley Hospital Clinico-Pathologic Conferences). WARD, D. F., [U. S. N. R.] *J. Iowa M. Soc.*, **34**:16-18. 1944.

A case report. A review of the literature revealed that the incidence of benign gastric tumors in two of our great clinics was identical, 1.3%, among gastric resections for tumor. Necropsy statistics indicate a greater incidence. Clinically, 10% of the patients have pyloric obstruction. The symptoms of dyspepsia are absent or mild, and the patient's health affected but little. Roentgenologically, a punched out, circumscribed defect is observed over the gastric walls, leaving the curvature regular and pliant. These tumors cause little or no peristaltic disturbance, and retention is slight except when the lesion is at or near the pylorus. Malignant transformation occurs in about 13% of these tumors. Simple excision may be adequate, but more radical surgery is demanded if histological examination reveals malignant change.—M. E. H.

Acute Dyspnea in a Case of Carcinoma of the Stomach. CHIDESTER, A. B. [Auburn, N. Y.] *New York State J. Med.*, **43**:1441. 1943.

This is a case history of a woman in her sixth month of pregnancy, on whom necropsy revealed a carcinoma of the stomach with metastasis to the liver and the adjacent glands.—J. L. M.

Malignant Tumors of the Stomach. DEAMESTI, F. [Univ. of Santiago, Santiago, Chile] *Am. J. Surg.*, **63**:78-85. 1944.

A report on 127 cases of malignant gastric tumors. Gastric resection was done in 58 of 104 patients subjected to operation (55.76%) with a mortality of 20% (16% in subtotal, and 44% in total gastrectomies).—W. A. B.

The Outlook on Carcinoma of the Stomach. THORSTAD, M. J. [Harper Hosp., Detroit, Mich.] *Am. J. Surg.*, **64**:242-247. 1944.

This is a study of 970 patients with cancer of the stomach, the records being taken from two hospitals. Clinically, inoperable cancer was found in 42.3% of patients at Harper Hospital, and in 76.6% at Receiving Hospital. At the latter institution gastric resection was done in but 9.8% of cases, and at the former in 19.4% with a mortality rate, during 1941 and 1942, of 29%.—W. A. B.

Carcinoma of the Large Bowel. MCGAULEY, F. F. [Schenectady, N. Y.] *New York State J. Med.*, **43**:1727-1731. 1943.

In discussing cancer of the large bowel, the author presents the subject under these headings: (1) diagnosis and treatment of cancer of the large bowel; (2) review of 58 cases seen by the author during the past 10 years (12 of 28 patients are still alive for unstated periods after operation); (3) importance of high operability in cancer of the large bowel; and (4) presentation of 2 unusual cases, each with a paucity of diagnostic symptoms.—J. L. M.

The Early Diagnosis of Carcinoma of the Colon. CROHN, B. B. [Mt. Sinai Hosp., New York, N. Y.] *New York State J. Med.*, **43**:1719-1723. 1943.

The author emphasizes that one should not overlook the possibility of carcinoma in any patient at any age with symptoms relative to the gastrointestinal tract. Hereditary factors, or at least familial tendencies, are pointed out.

About two-thirds of all carcinomas of the colon can either be felt by the examining finger or by the sigmoidscope, and in that area they are the most difficult ones for the x-ray to demonstrate. An x-ray examination is justified only after a thorough physical examination.

In the etiology of carcinoma of the colon no single factor is more momentous than the existence of adenomatous polyps, single or multiple, or of well-developed generalized polyposis, particularly of the congenital type. Sooner or later in the life of the bearer, congenital polyposis of the colon undergoes malignant transformation in practically 100% of the cases. Such malignant metaplasia is not accidental, for carcinoma may be seen not in one area alone but in several. Any polyp of the large bowel is susceptible to carcinomatous change, particularly if it is situated at a point of greatest mechanical friction, such as the rectosigmoid angle or rectum. Every polyp of the rectum or rectosigmoid angle should be fulgurated or snared, whether the biopsy be positive or negative, for every polyp is essentially suspicious and potentially capable of providing the basis for a carcinomatous neoplasm. A biopsy specimen taken from a large polyp may at the first or even the second attempt be reported as benign in nature, yet this does not exclude the possibility of beginning malignant transformation at some other aspect of the same polyp.—J. L. M.

Peritonitis Secondary to Perforation in Carcinoma of the Colon. ALLEN, P. D. [New York, N. Y.] *New York State J. Med.*, **43**:1732-1735. 1943.

Perforation of carcinoma of the colon resulting in local or spreading peritonitis is more common than is ordinarily suspected. It may occur either at the site of the carcinoma or in the loop of bowel just proximal to it, and is more likely to occur in the rapidly growing, fungating type of adenocarcinoma. The diagnosis should always be considered in persons of cancer age who show evidence of peritoneal inflammation, in spite of the absence of other signs of malignancy. As an emergency procedure more frequent stool examinations for blood will give a hint to the diagnosis. X-ray examination in the nonemergency case should be accurate if the proper technic is employed to study the mucosal pattern. Treatment should aim at drainage of the abscess and later resection. Prognosis is extremely poor, as treatment can usually be only palliative. Seven case reports are presented.—J. L. M.

The Diagnosis of Carcinoma of the Right Colon. CONNOR, G. J., and HARVEY, S. C. [Yale Univ. Sch. of Med., New Haven, Conn.] *Yale J. Biol. & Med.*, **16**:289-300. 1944.

A series of 50 cases of carcinoma of the right colon was analyzed with respect to the important symptoms and signs. Emphasis was placed on the findings that should lead to a suspicion of the disease. Abdominal discomfort and weakness were common manifestations. A change in the bowel habit cannot be relied upon as a diagnostic sign, since 36% of the cases showed no such change. A gross change in the character of the stools was not common. The presence of occult blood in the stools was demonstrated in 75% of the cases in which an examination was made. Intestinal obstruction was not frequent unless the ileocecal valve was involved. Under such circumstances it may be an early manifestation of the disease. A palpable abdominable tumor was noted in 82% of the resectable cases. Mild tenderness was frequently present in the region of the tumor. The majority of the cases showed evidence of secondary anemia, but the degree of the anemia was of little assistance in evaluating the extent of the tumor. In 8 of the 50 cases the correct preoperative diagnosis of carcinoma of the right colon was not made.—J. L. M.

Carcinoma of the Right Colon. HARVEY, S. C., and CONNOR, G. J. [Yale Univ. Med. Sch., New Haven, Conn.] *Connecticut State M. J.*, **8**:286-288. 1944.

The authors believe one-stage colectomy with immediate anastomosis is a superior method of treatment for carcinoma of the right colon, and that it can be utilized with a reasonable risk provided it is carried out precisely with attention to certain fundamental principles.—M. E. H.

Present Status of Cancer of the Colon and Rectum. SUGARBAKER, E. D. [Columbia, Mo.] *J. Missouri M. A.*, **41**:49-53. 1944.

The importance of careful preoperative evaluation and care is stressed. Radical surgery is the treatment of choice for all cancers of the colon and rectum. Future improvement must come through earlier diagnosis and a better understanding of the precancerous role of polyps.—M. E. H.

Anterior Resection for Carcinoma Low in the Sigmoid and the Rectosigmoid. DIXON, C. F. [Mayo Clinic, Rochester, Minn.] *Surgery*, **15**:367-377. 1944.

An operative technic is described. The superior hemorrhoidal vessels may be sacrificed without apparent impairment of the circulation to the rectosigmoid or rectum. Among 181 patients who underwent anterior resection with view to cure (87.9% of total) the mortality was 12.1% with only 3 postoperative deaths in the last 76 cases. One hundred and four patients survived, and of 102 patients followed, 60 (58.8%) survived for more than 3 years.—W. A. B.

Carcinoma of the Rectum. Conclusions Based on 12 Years' Experience with Combined Abdominoperineal Resection. COLLER, F. A., and RANSOM, H. K. [Univ. of Michigan, Ann Arbor, Mich.] *Surg., Gynec., & Obst.*, **78**:304-315. 1944.

A clinical discussion.—J. G. K.

The Surgical Pathology of Rectal Cancer. DUKES, C. E. [St. Mark's Hosp., London, England] *Proc. Roy. Soc. Med.*, **37**:131-144. 1944.

The author has studied the size, position, and histological character of the primary tumor, and the extent of local, venous and lymphatic spread, in specimens obtained from more than 1,000 cases of carcinoma of the rectum treated by excision, and has followed the subsequent history of the patients.—E. L. K.

Carcinoma of the Rectum. Conservative Surgery in Certain Instances. KELLER, D. R. [Medical Corps, U. S. N. R.] *Am. J. Surg.*, **64**:346-351. 1944.

Report of a case showing early malignant change in the base of a rectal polyp removed by local excision.—W. A. B.

Carcinoma of the Rectum. MCCORMICK, N. A. [Metropolitan Hosp., Windsor, Canada] *Radiology*, **42**:531-538. 1944.

An analysis of 83 cases of carcinoma of the rectum is made with a discussion of types of treatment. Operation is recommended when at all possible. Operative mortality is decreasing and at present is about 10%. Preoperative radiation is recommended, and careful preoperative preparation is particularly important. Palliative x-ray has been used with definite improvement in 70% of cases. Combined x-ray and interstitial radiation is occasionally used as a curative procedure. Colostomy is necessary only with impending obstruction.—R. E. S.

Indications for Conservatism in the Surgical Treatment of Rectal Cancer. PACK, G. T., and GALLO, J. S. [Memorial Hosp., New York, N. Y., and Paterson General Hosp., Paterson, N. J.] *J. M. Soc. New Jersey*, **41**:85-90. 1944.

The authors have performed 17 conservative rectal operations by one or another of the 3 technics described. Two of the patients died with hepatic metastases; 15 patients were living and well 6 weeks to 4 years after operation.—M. E. H.

Ruptured Mucocele of the Appendix with Pseudomyxoma Peritonei. TIMONEY, F. X. [St. Vincent's Hosp., New York, N. Y.] *Am. J. Surg.*, **64**:417-419. 1944.

Case report.—W. A. B.

Book Reviews

VIRUS DISEASES IN MAN ANIMAL AND PLANT. A Survey and Reports Covering the Major Research Work Done During the Past Decade. Gustav Seiffert. Translated by Marion Lee Taylor. Philosophical Library, New York, N. Y. 1944. 332 pp. Price $5.00.

According to the preface, the author's purpose in writing this book is to introduce the newcomer to the virus problem, to assist the investigator by a list of references, and to encourage further penetration into the subject of viruses. To accomplish these aims he presents a general discussion of viruses in general, of diseases caused by viruses and "virus-like organisms", and of methods used in virus studies.

The author's effort is in vain because of the exceedingly poor translation. The book is such a mixture of poor English, incorrect terminology, and misspelled words that the newcomer will be discouraged and the investigator mystified.

It is regretted that these imperfections obscure the author's meaning and prohibit a review of the work.

The book can be recommended only as a partial reference to the literature up to the year 1938.

H. B. Andervont.

THE RIDDLE OF CANCER, Charles Oberling, M. D. Translated by William H. Woglom, M. D. Yale University Press, New Haven. Humphrey Milford. Oxford University Press, London. 1944. 196 pages. Price $3.00.

This is a translation from the French of a book that has already been comprehensively and objectively reviewed in this journal (*Cancer Research* **3**:350-352. 1943) by Woglom, who has now translated it. It may be said at once that the translator has succeeded in preserving the interesting and skillful presentation of the subject that distinguished the original. The third chapter, for instance, which gives an account of the 3 hypotheses advanced in the past to explain cancer, namely the irritation, the embryonic, and the microbic hypotheses, reveals not only the extensive knowledge of the cancer problem that might be expected from one who is a pathologist of the French school and who has himself made valuable contributions to the subject, but also a grace of style rarely to be found in scientific medical writings. It seems to be a gift conferred as a birthright upon French writers. The English edition is an improvement on the French. A number of minor errors and inaccuracies have been corrected; an index has been added; and an extensive enlargement of the bibliography, which now occupies no less than 18 pages, comprising over 400 original contributions, enhances the value of the book.

The book will therefore be read with pleasure by those actively interested in the cancer problem, who can bring their own critical judgment to bear on the author's statements and views. Particularly happy are the early chapters, dealing with the history of cancer research. There Oberling brings back the striking personality of Borrel, one of his teachers, who combined the intuition of an artist with the unremitting quest of the scientist for evidence to justify his visions.

Yet the book is intended to appeal to a wider audience, and for this reason the very qualities that make its reading attractive compel one to point to serious shortcomings. Only a few can be mentioned, since the complexity of the subject demands a detailed discussion.

In the introduction Oberling states frankly that his book is written as a justification of the virus hypothesis of cancer and accordingly will displease many of his colleagues. But it may be asked why such a justification should be necessary, for both in this country and in England this conception has been accepted by many as a working hypothesis, and active research has been carried out along this line by numerous workers. It must be remembered, however, that Oberling wrote his book for a French audience. Although France may be said to have been the birthplace of the virus hypothesis, where Borrel formulated it 40 years ago, it has never received serious consideration there, not even after the experimental demonstration by Rous and his collaborators of the existence of malignant tumors transmissible from one fowl to another by a virus-like agent and the subsequent confirmation of this fact by other workers.

Oberling ends his book by admitting that the virus hypothesis of cancer remains unproved, but says that it has justified itself as a working hypothesis by the stimulus it has given to experimental work. That is a fair statement, and in this country few will be disposed to quarrel with it. He might have gone even further. The existence of an agent that, when brought into contact with a normal cell, closely integrated with the commonwealth of cells constituting a living organism, is capable of disrupting it from this union of cells and conferring upon it all those qualities comprised by the term *autonomy* is in itself a biological phenomenon of profound significance. It has a general significance, and it has an immediate special significance to the student of cancer. For here the transformation of a normal cell into a malignant one of a type that can be accurately predicted takes place almost immediately. In the experimental production of cancer by such agents as chemical carcinogens, or by hormones, we can follow the long drawn out preliminary stages in detail, but this final episode remains hidden. In other words the virus tumors enable us to isolate this culminating stage from its long and varied preliminaries. The question at issue is therefore: Does the process as we see it in the virus tumors represent the prototype, the exact pattern, of the final stages through which all cells pass when they become malignant? Oberling admits that this question has not yet been answered, but, he adds, only the virus hypothesis can explain satisfactorily "the chief characteristic of the true neoplasms: Autonomy." With this statement he leaves the firm ground of science and becomes an advocate.

His attitude is very different from that of one who has taken a leading part in establishing the virus theory of cancer, and who cannot well be accused of prejudice against it. Peyton Rous ends his Harvey Lecture, entitled "The Virus Tumors and the Tumor Problem," with the following sentences: "How far should one be led by

the assumption that certain tumors may be due to viruses? Only so far as to make tests with these growths. The tumor problem has withstood the most corrosive reasoning. Yet since what one thinks determines what one does in cancer research, as in all else, it is well to think something. And it may prove worth while to think that one or more tumors of unknown cause are due to viruses."

The qualities and skill of the author as an advocate shine most brightly when he deals with the transplantable tumors of the mouse and the rat. These tumors present evidence against the conception of a virus origin for all malignant tumors that has so far proved resistant to both experimentation and argumentation. And so the able advocate proceeds to discredit them.

He quotes a number of investigations on transplantable tumors in which certain procedures have given favorable therapeutic results, though their application to spontaneous tumors in man or in animals resulted in failure. Oberling then continues: "By sad experience they have learned that transplantable cancer is not spontaneous cancer; that facts applicable to the one do not touch the other; that, paradoxical as this may be, an animal into which a cancer has been inoculated is not a cancerous animal. The cancerous animal has produced his own tumor, his body has undergone all those changes that led gradually down to its development, and it is his own cells that have suffered the malignant transformation. The animal bearing a transplanted neoplasm, on the other hand, is but a culture medium for cells that are not his own, and toward which he consequently reacts in a totally different way.

"As a result, interest in the questions that transplantable tumors were once expected to solve has inevitably fallen off, for more must never be demanded of a method than it can give. Altogether they have turned out to be a grand illusion, for so little do they resemble the spontaneous new growths that they are utterly incapable of furnishing information applicable to man, or of providing the least insight into the cause of the malignant change, since they were already established from the first. Begun with enthusiasm, the investigation of transplantable tumors ended in woeful disappointment."

With this sweeping condemnation Oberling removes at one stroke a body of evidence that has consistently stood in the way of his thesis, since the most searching investigations carried out with these transplantable tumors have failed to give any evidence of the existence in them of an infecting agent. But at the same time he also destroys the evidence on which our present conception of the nature of cancer rests, namely the autonomy of the cancer cell. Oberling agrees that autonomy is the essential feature of the cancer cell. But this conception is not self evident, and at the time the work with transplantable tumors was begun its validity was hotly contested. It was established, as will be explained presently, on the evidence presented by the transplantability of malignant new growths. I have failed to find in Oberling's book any evidence on which *his* dictum on the autonomy of cancer cells rests.

Having taken part in this early work on transplantable tumors I ought to remember the "sad experience" and the "woeful disappointment." But I do not. My recollection is that this work on transplanted tumors, by establishing the autonomy of the cancer cell and the ability of a malignant tumor to grow "out of itself" without infecting the normal cells of the organism in which it grows, was hailed as an important advance in our knowledge of cancer.

If my evaluation of this line of investigation is considered to be biassed, because I took part in it myself, I will call first, as a witness from the past, an eminent surgeon of that period who was a deeply interested spectator of the experimental work: Sir Henry Butlin. At the beginning of the century, when this was being carried out, Butlin was one of the leading English surgeons. Believing in the local origin of cancer and its autonomous growth, a view which, as just mentioned, was not generally accepted in the early days of his career, he had tried to establish the curability of cancer by operation at the earliest possible stage of the disease, but had met with a good deal of passive opposition. Towards the end of his life he wrote a small book on cancer that was published in 1912, shortly after his death, in which he described the impact of the experimental work on clinical thinking in the following passage. After recounting the humoral and the constitutional theories of the etiology of cancer, which at the end of last century were held by many clinicians, Butlin continues as follows:

"Under this pessimistic pathology the most that was ever expected from an operation was that the patient might die a little less miserably. The disease was often advanced before it was removed; the operation was quite inadequate. . . . There was no hope either for the present or the future. To the very end of their surgical lives, many surgeons of the surgical generation before my own were . . . under the influence of these views, and I have heard the expression many times: 'Once cancer, always cancer.'

"I do not remember when, or where, or how the theory of the local origin of cancer came before the pathologists and surgeons. It was a very happy inspiration, and humanity has reason to be very thankful for it. I have no recollection of discussing it, and suddenly being struck with the belief that it was true. Probably conversion came slowly from the more careful study of individual cases of cancer and from the slow discovery that operations were more successful than they had been believed to be. I can well remember occasionally drawing the attention of the permanent staff [of St. Bartholomew's Hospital] to such successful cases. The reply was always: 'Well, you may be sure it was not a case of cancer.' . . . Gradually belief in the curability of cancer was established. Hope was infused into the minds of surgeons and their patients. . . . It must not be imagined that all this was accomplished without a great deal of opposition, or that it was carried through in the course of a few years. Even when it was evident that the humoral theory could no longer be maintained, it was by no means abandoned. The old humoral pathologists, and those who would not admit the local origin of cancer, spoke of the constitutional origin of cancer; and discussions took place and battle was waged with varying success by the adherents of the two theories, and would probably still be waging had not the question been definitely settled by experimental investigation . . . in the course of the last ten years.

"Since then the local origin of cancer holds the field.

The object of the surgeon is to remove it early while it still remains a local disease. . . . His working theory is plain and simple: it is to remove the whole of the existing disease—in fact, to get all the cancer cells out of the body of his patient. If he can do this, the patient will be cured. . . . The advantages which have been gained for cancerous persons by the institution of a good working theory for a bad one are greater than the mind of man could have conceived."

Here are two experts looking at the same subject and arriving at conclusions that could not well be more different, an interesting comment on how history is written. While neglecting to discuss this highly significant aspect of the work with transplantable tumors Oberling turns to what may be called the scrap heap of experimental cancer research. He gives a good deal of space to a consideration of alleged therapeutic results with transplantable tumors that could not be verified when applied to spontaneous growths. But they could not even be confirmed when the experiment was repeated with appropriate controls on transplanted tumors. For one reason or another the experiments were faulty. Similar claims of alleged therapeutic results have been made by clinicians for human cancer, but could not be confirmed when tested critically. Faulty work like this is thrown into the discard, where it belongs and where it should remain.

On the other hand, when therapeutic agents effective in the treatment of spontaneous tumors in man, such as radium, are applied to transplantable tumors they react in essentially the same manner. Transplanted tumors are capable of forming metastatic growths. Another interesting phenomenon illustrating their essential similarity to spontaneous tumors is the specificity of the stroma reaction. The inoculated cancer cells elicit from the normal animal a connective tissue reaction leading to the formation of a stroma identical in its morphological appearance with the stroma of the spontaneous tumor. Here the normal animal reacts to the inoculated cancer cells in exactly the same manner as the cancerous animal. In many, though not in all respects, therefore, the transplanted tumor closely resembles the original spontaneous tumor, and the wholesale condemnation pronounced by Oberling is not justified.

But these are almost minor criticisms compared with the basic flaw in Oberling's views, his failure to appreciate the main import of the transplantability of mammalian tumors. From the beginning the question was asked whether in the transfer of these tumors from one animal of mixed parentage to another of a different mixed parentage, but of the same species, the cells of the daughter tumors were direct descendants of those that had been introduced in the inoculum or whether they arose from the tissues of the host. To put the problem more simply: Is the transfer a transplantation or an infection? The importance of deciding between these alternatives was recognized from the very beginning. Jensen's work, published in 1903, was of special value in this connection, because he had laboriously followed the fate of the introduced cells and demonstrated that the new tumors derived exclusively from them and were not due, not even partly, to an infection of the cells of the new host. His results were confirmed by Bashford and his collaborators. Hundreds of other experiments were carried out then, and thousands have been made since, with the object of determining whether transmission of these tumors is possible without the intervention of living cells. Every known device was used to exclude the presence of living cells, and whenever this had been accomplished all such attempts gave consistently negative results.

While this outcome cannot be said to have disproved conclusively the presence of a virus, since negative results cannot be accepted as definitive and could conceivably be accounted for by postulating a subsidiary hypothesis, it certainly does not lend any support to the virus conception. What is, however, much more important is that this extensive body of evidence established the fact that in mammals the force that drives the cancer cell on to its malignant neoplastic growth resides within the cancer cell and is intimately bound up with it, so that the cancerous tumor grows entirely "out of itself" and without infecting the neighboring cells of the surrounding tissue.

This is a fundamental fact on which our conviction of the curability of cancer is based. For when the immediate cause of cancerous growth lies within the cell and is inseparable from it, cancer can be cured by removing all the cancerous cells. And all can be removed at the beginning of the disease when they are localized to its site of origin. The proof of the pudding is in the eating. Almost every month surgeons publish series of cases, treated by them over a period of years, showing results that conform to this conception. From the viewpoint of practical results the work on the transplantable tumors of mammals is at least equal in importance to any line of cancer research that has been followed since.

While Oberling is correct in stating that "an animal into which a cancer has been inoculated is not a cancerous animal," he commits an error in omitting to state that this had been recognized at a very early stage of the work with transplanted tumors. It became evident the moment it was established that the transplanted cancer grew entirely from the cells of the inoculum, and was pointed out 30 years ago again and again in the writings of Bashford. This very fact that cancer cells, when removed from the environment of an animal, "A," of mixed parentage in which they had originated, would continue to grow in thousands of normal animals of a different mixed parentage, in which the normal tissues of animal "A" would not grow, established what Oberling himself describes as "the chief characteristic of the true neoplasms: Autonomy." He fails to realize this when he asserts that transplantable tumors are utterly incapable of furnishing information applicable to man. In denying that transplantable tumors can provide the least insight into the cause of the malignant change he forgets also that the conception of a virus of cancer is based on experiments with certain transplantable sarcomas of the fowl. After they had been transmitted by means of living cells through a number of successive tumor generations they began to be transmissible by cell-free extracts. The transplantable tumors of the mouse and the rat do not behave in this way, nor do many other transplantable fowl tumors that have been tested. They must therefore be ignored as a "grand

illusion," but transplanted tumors that become transmissible by cell-free filtrates are welcomed. Oberling, the advocate, pleads in a court in which Oberling, the judge, does not admit hostile witnesses.

Considerable importance is attached in the book to the phenomenon of immunity to cancer and to the numerous attempts made to exploit it for therapy. Here again no reference is made to the earlier extensive investigations, carried out as soon as the phenomenon had been discovered, which established the fact that it is not a specific immunity to cancer cells at all but a reaction of the organism to the transfer of cells, either normal or malignant, from one animal to another animal of the same species. As early as 1908 Bashford and his associates pointed out that the term "immunity" is misleading and should be replaced by the more accurately descriptive term "resistance to transplantation." It is not possible to give a detailed account of this work, which has been fully reviewed by Woglom in his monograph on experimental cancer, published in 1913. But a few findings may be mentioned, such as that a spontaneous tumor can develop in an "immune" animal; that "immunization" is ineffective against an autoplastic transplantation of a spontaneous tumor and against its metastatic dissemination; and that the growth of even a transplanted tumor cannot be arrested by immunization. If Oberling had been acquainted with this work he could not have said that it seemed "fraught with boundless possibilities."

Subsequent workers ignored these warnings and asserted that they obtained therapeutic results. But whenever their experiments were repeated they could not be confirmed and in reviewing the later work on immunity, carried out since 1913, Woglom writes as follows:

"Of these 600 communications a small number are of permanent value, many record unconscious and unnecessary repetitions of previous experiments, and far too large a proportion are merely ridiculous. . . . It is to be feared that the famous advice 'Don't think, try the experiment' is often too literally followed." Oberling mentions Lumsden as having succeeded in preparing a serum that was selectively toxic to cancer cells but not to normal cells, quoting a paper published in 1931. This work was repeated in 1937 by Phelps, who found that the serum was equally toxic to cancer cells and to normal cells and Lumsden retracted his assertions, but no reference is made in the book to these two papers.

The criticisms that I have felt compelled to make must not be interpreted as directed against the virus hypothesis of cancer. In view of the existence of the filterable tumors such a hypothesis cannot be excluded as *a priori* untenable. The conception of some viruses as macromolecular chemical substances, appearing as abnormal products of cells, has found favor in recent years among many virusologists, and it has much to recommend it when applied to cancer. It would resolve many of the difficulties that are encountered as long as we conceive the virus as a foreign biological entity infecting the cell. But this last conception of the cancer virus is the one that Oberling insists on and he dismisses the alternative conception curtly by saying that it is "manifestly false." No scientific arguments are adduced to justify this statement. I can see nothing "manifestly false" in it.

My objections are pointed against the tendency to exalt theories over facts, to make facts fit into the Procrustean bed of a theory. If the facts do not fit, they can be stretched by the addition of subsidiary hypotheses or, what is worse, they are mutilated.

While writing this review I have come across the following statement: "I have the feeling that we shall always find a catch somewhere, as I suppose the alchemists always did when it came to the final moment of projection. The problem may become more and more meaningless as we seem to come nearer to it, or perhaps it will become obvious that it is not one which could ever be solved by beings like ourselves. However, this really does not matter, for we can be certain of one thing: Whatever the final outcome of inquiries . . . there is an immense amount waiting to be found out on the way." This passage does not refer to cancer. It was found in a lecture on "Brain Mechanism" by E. D. Adrian (*Science,* May 5th, 1944, p. 357). Very much the same can justifiably be said about many other biological problems. Cancer is also essentially a biological problem, and I fear that a person who reads Oberling's book may get an impression similar to that voiced by Adrian.

In a purely academic line of biological research there may be no touchstone by which the value of theories that have been formulated can be assessed. But cancer is not only a biological problem, it is also a disease facing us with actual and practical problems. It faces us with the grim fact, against which any theoretical considerations formed on the basis of scientific investigations can be tested, that in the absence of treatment the patient will surely die. The cancer problem has become more and more complex, but it has not become more and more meaningless. We know that cancer is due to an intracellular change, by which autonomous growth is conferred upon a normal cell. We do *not* yet know the exact nature of the change, but in spite of this gap in our knowledge we can induce the change experimentally in animals; moreover, we can induce it by agents that elicit the disease in man. In other words, we can "cause" the disease. We can also cure the human disease, and the conditions under which it can be cured are well understood. These are facts that have been established in spite of our ignorance of the nature of the intracellular change, and they will persist whatever its nature is eventually found to be.

In order to improve the results obtained in the treatment of cancer by earlier diagnosis it is necessary to gain the confidence of the medical profession and of the patient. We are not likely to succeed if we persist year in and year out in describing cancer as an unsolved riddle.

W. Cramer.